CENTER FOR MEDICARE AND MEDICAID SERVICES

Medicare Coverage Advisory Committee

Meeting of the Medical and Surgical Procedures Panel

June 12, 2002

Baltimore Convention Center

One West Pratt Street

Baltimore, Maryland

Panelists

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Adjournment

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PANEL PROCEEDINGS

(The meeting was called to order at 8:08 a.m., Wednesday, June 12, 2002.)

MS. ATKINSON: Good morning, and welcome, committee chairperson, panelists and guests. I am Michelle Atkinson and I am the executive secretary of the Medical and Surgical Procedures Panel of the Medicare Coverage Advisory Committee. The panel is here today to hear and discuss evidence regarding deep brain stimulation for Parkinson's disease. In evaluating the recommendations presented to you today, CMS encourages the committee to consider all relevant forms of information, including but not limited to professional society statements, clinical guidelines and other testimony you may hear during the course of this committee meeting.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of impropriety. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. To determine if any conflict existed the Agency reviewed all financial interests reported by

the committee participants. The Agency has determined that all members may participate in the matters before the committee today

With respect to other participants, we ask in the interest of fairness that all persons making statements or presentations to this committee disclose any current or previous financial involvement with any firm whose products or services they may wish to comment on. This includes direct financial investments, consulting fees, and significant institutional support.

I call your attention to the invited speakers, who are not part of the panel, but will be part of our discussion. Also, due to circumstances beyond her control, our temporary industry rep, Christine Grant, will not be available until the afternoon session.

And I would now like to turn the meeting over to Dr. Steve Phurrough, who will give his opening remarks, then Chairman Dr. Alan Garber, who will ask the panel members to introduce themselves and to disclose, for the record, any involvement with the topics to be presented.

DR. PHURROUGH: Thank you, Michelle.

I'm Steve Phurrough. I am presently the

division director of Medical and Surgical Services in the Coverage and Analysis Group. We are the division that is looking at this particular issue. And, for a few weeks, I'm the acting director of Coverage and Analysis. Sean Tunis is serving as the acting chief medical officer for CMS.

On behalf of CMS, we would like to welcome you here and thank you for your willingness to serve on this panel and to assist us in giving us advice on the level of evidences that we have here for this particular issue.

I also thank the speakers for their attendance and their willingness to assist us in providing us information.

With that, Alan?

DR. GARBER: Thank you, Steve.

I want to second what Steve just said and thank the speakers and panelists for taking the time to attend the meeting today.

The panel had a conference call recently to help go over the questions and to clarify the questions that the panel will be asked to address, and I think that that effort was very successful. In trying to formulate the questions, it was very tempting -- at least for me, and I think for others,

as well -- to try and think about the -- and get into discussions of the substance, but we largely avoided -- we did avoid discussing the substance of the questions. And by that, I mean we didn't begin the deliberations early. Yet I think it gave us a clear idea of where we think the questions need to go and what kinds of -- what kinds of topics are likely to come up today in the discussion.

I do hope that -- I know that people have planes to catch and so on, and I'm going to try to keep us very tightly to this schedule and, if at all possible, actually to move quickly, where we have opportunities to move quickly. And I just want to urge all the speakers not to exceed their allotted time. So we'll be very strict about enforcing that.

And, with that, I'd like to just turn it over to our first speaker, who is Perry Bridger, from CMS.

MR. BRIDGER: Thank you. Good morning, and thank you.

Chairman Garber, distinguished panelists, invited guests, and members of the public, it is an honor to present to you today on behalf of the Deep-brain stimulation Analysis Team at the Centers for Medicare and Medicaid Services.

For the next ten minutes or so, I'm going to briefly describe Parkinson's disease, discuss with you the history of Medicare coverage for deep-brain stimulation, give a quick overview of the current coverage request, present the voting and discussion questions that will be your focus today.

Finally, I'll introduce Dr. Perry Cohen, who will be reading Dr. Barry Green's statement. Dr. Green is the requestor of this national coverage termination request and could not be here today to address you.

The CMS Review Team that has been working on this issue, are myself, lead analyst; Dr. Larry Schott, a neuro-radiologist and our lead medical officer; Dr. Steve Phurrough; Michelle Atkinson, our executive secretary, who you know well; Tanisha Carino, and William Larson.

Very briefly, Parkinson's disease is age-related, chronic, neurodegenerative disease whose underlying abnormality is the progressive loss of dopamine-producing cells in the brain, generally characterized by the symptoms of tremor, rigidity, bradykinesia, and postural instability.

The onset of idiopathic Parkinson's disease most often occurs between the ages of 45 and

65. And currently, there is no known cure, although research for neuro protective and restorative therapies are underway. Currently, only symptomatic therapies are available.

Levodopa remains the gold standard for treatment used on concert with other agents such as dopamine agonists and anticholinergics. Surgical lesioning therapy and deep-brain stimulation are -- generally considered after medical treatment cannot adequately balance control of the disease with the side effects of the medication.

Medtronic will be presenting to you shortly, but I just briefly want to explain that deep-brain stimulation is the stereotactic placement of an electrode and delivery of electrical stimulation to certain areas of the brain. In general, it's thought that the high-frequency stimulation of the neuron induces functional inhibition, and deep-brain stimulation simulates the effect of a surgical lesion, but does not deliberately destroy the tissue.

The Medtronic Activa Tremor Control System PMA was approved in July of 1997 for a unilateral thalamic stimulation for tremor suppression, and a recent supplement was approved for bilateral globus

pallidus internus or subthalamic nucleus stimulation for other Parkinson's symptoms. Celia Witten is here from the FDA and will be explaining a little bit to you about the FDA process, and go more in depth about the approvals for the device.

In 1997, Medicare amended our national coverage policy for the treatment of motor function disorders with electrical stimulation, which are currently not covered, to allow our contractors the discretion to cover deep-brain stimulation. And currently, all Medicare contractors cover unilateral thalamic stimulation, and many Medicare contractors cover bilateral stimulation of the STN or GPi.

Our current request was initiated by Barry Green, a Parkinson's patient in Texas, a state where Medicare does not currently cover the bilateral indication. The request was formally accepted for a national-coverage determination on October 19th, 2001.

The current request has prompted us to consider both the unilateral and bilateral indications for use of this modality. In addition, we obtained a BlueCross and BlueShield Technology Evaluation Center technology assessment of deep-brain stimulation. And Joan Vatz, the primary

assessor, will be presenting that assessment to you later in the morning.

The panel has received the following materials, all of which are publicly available, many of them on our Web site. A complete set of the material is also available on the desk outside of this room.

You have had the opportunity to read the technology assessment, the unilateral study description, and other materials related to deep-brain stimulation. After hearing public comments and scheduled commentaries presented here today, you'll be asked a series of voting and discussion questions, and I'd like to briefly outline those for you now.

The first question the panel will discuss is the following. Is the evidence adequate to determine the clinical effectiveness of bilateral subthalamic nucleus deep-brain stimulation for a well-defined set of Medicare patients with Parkinson's disease? If the evidence is adequate, what is the size, if any, of the overall health effect of this intervention?

We have asked you to use the MPAC's own categories of effectiveness, which I will review for

you after I present the remaining two voting questions.

And I'd just like to read these into the record. Panel Voting Question Number 2. Is the evidence adequate to determine the clinical effectiveness of bilateral GPi DBS for a well-defined set of Medicare patients with Parkinson's disease? And if that evidence is adequate, what is the size, if any, of the overall health effect?

Panel Voting Question Number 3 relates to the unilateral indication and asks, is the evidence adequate to determine the clinical effectiveness of unilateral thalamic DBS for essential tremor and/or Parkinsonian tremor for a well-defined set of Medicare patients with Parkinson's disease? And if the evidence is adequate, what is the size, if any, of the overall health effect?

The following are the categories of effectiveness, as previously determined by the MPAC, and there are seven categories: breakthrough technology, technology is more effective, as effective but with advantages, as effective and with no advantages, less effective but with advantages, less effective but with no advantages, and not effective.

In addition to the voting questions that I've just described, we have posed to you three discussion questions not directly addressed by the scientific evidence that we would like the panel to discuss, and they are the following. Available clinical evidence evaluates bilateral STN or GPi deep-brain stimulation in early-onset Parkinson's disease patients. Can these results be generalized to late-onset advanced Parkinson's disease patients?

Discussion Question 2. For coverage purposes, should Medicare patients be considered candidates for unilateral thalamic or bilateral STN or GPi DBS only if their characteristics closely match those of the patients included in the available study?

And, finally, Discussion Question 3. DBS, in the clinical literature, is performed by highly trained providers at experienced facilities. Should facility and provider criteria to perform DBS in Medicare patients be part of any positive coverage decision?

I would like to thank all of the panel and all of the participants in today's meeting for devoting their time and effort to this very important topic.

At this point, I'd like to introduce Dr. Perry Cohen, who will be reading Dr. Barry Green's statement into the record for you. Dr. Cohen?

DR. COHEN: Thank you.

My name is Perry Cohen and -- another Perry. I've been asked by Barry Green to read his statement. He is in Texas in the -- I think he's recently undergone surgery and is not available to make the statement himself.

I have my own opinions on the subject, but these are all Barry Green's -- this is entirely Barry Green's statement. I had previously served on -- as patient representative on the FDA panel that reviewed deep-brain stimulation about two years ago.

Members of the panel, invited guests and audience, I want to thank you for the opportunity to address you in this public forum. I am the national requestor for the adoption of coverage by CMS for the bilateral subthalamic nucleus deep-brain stimulation.

As revised on January 7th, the bilateral deep-brain stimulation of the globus pallidus interna was included. After further consideration, they are also evaluating the unilateral thalamic stimulation for essential tremor and Parkinson's

Tremor. They have renamed the title of the study the "Deep-Brain Stimulation, DBS, for Parkinson's disease."

As the advocate for many fellow patients, I want to offer constructive suggestions for dealing with the process undertaken. The exact time frames can be readily seen in the Table of Actions and tracking data at the end of this presentation. One, quality of operations, the equipment to be utilized, and the patient. I think the operations or procedures used by each surgeon, the operating facility, and the company chosen to supply the special equipment should undergo a general test of applicability for each individual. Any state agent or other agency spending national Medicare dollars should provide the results of the test of applicability.

Meaning: This would apply to all decisions made by the Medical and Surgical Procedures Panel of the Medicare coverage committees.

Two, cost of unilateral versus bilateral operations. The cost appears not to be considered a factor in the CMS decision between unilateral and bilateral DBS. I suggest that those laser

bilaterals are not the same bilaterals that are being considered in the procedures and should not have been used in comparative studies. Because the operation is slated as costing from $60,000 to $80,000 -- my own operation cost $80,000 at Presbyterian Hospital, and the doctors have not been paid as yet -- it would seem to me that Medicare would be concerned about this and, therefore, push for bilaterals, which is two unilaterals, but done during the same operation. Therefore, the cost would be far less than two independent unilaterals. You and I know that cost is always a factor when it comes to Medicare.

The research was completed by 17 groups sponsored by Medtronic, NIH, et cetera, which indicated that the study for the bilateral STN/DBS is clearly not and does not have the same problems that the laser bilateral pallidotomy had. Thus, the comparison was ill conceived. Furthermore, the cost for a unilateral ranged from $60,000 to $80,000. A bilateral is $85,000 to $90,000. It clearly seems that we should take the less expensive way to go.

In terms of time, the same is true. A single bilateral takes one hospital stay, whereas two bilaterals take two hospital stays. The

bilateral operation requires one framing of the head by the halo unit. The two unilaterals require the head frame to be put on twice on the same patient, and the hospital charges would be double.

Meaning: If carefully considered by this committee, the cost and effectiveness can be clearly monitored, and the cost to the patient and hospital may be kept at a minimum.

Three, the time it's taken from the request to the almost final resolution today. I would suggest that the committee should oversee that the potential two-year interval could have been completed in at least a year ahead of what had occurred, and probably earlier. Medicare should have maintained close ties with the FDA. These ties would have allowed the FDA's decision to be made more quickly. I feel strongly that CMS could have avoided the issue and some of its time by focusing on the January 14th date.

Meaning: The national panels of CMS should have stronger positive relationships, rather than an apparent adversarial relationship. The patient should be the one considered over any other indicator.

Four, complete, informative, and better

graphics for patient booklets. Overseeing patient booklets should have been one of the committee's major targets. The FDA was in the best position to force its study groups to prepare a better patient booklet. Each team of neurologists, neurosurgeons --

DR. GARBER: Excuse me, Dr. Cohen. You've exceeded the time. And I think this letter is very helpful, but I just want to point out that copies of the -- of this memo are in each panelist's portfolio, and I think they're out front for the -- oh, they're not? Okay, we will make copies available for members of the meeting.

DR. COHEN: Very well.

DR. GARBER: Pardon me?

DR. COHEN: Okay. I didn't write the letter.

DR. GARBER: No, I understand. I understand. I appreciate your willingness to come up here and present it --

DR. COHEN: Okay.

DR. GARBER: -- but we only have five minutes --

DR. COHEN: Well, would you like for me to stop here?

DR. GARBER: Yeah, if there are just a few brief comments you want to make, that would be fine now, but I think, since we all have copies of this, we can take a look at the memo ourselves.

DR. COHEN: I could make my own comments, but I don't know if that's in order here.

DR. GARBER: No, I -- you may later on today, when we --

DR. COHEN: Okay. Well, there's just one more item here.

So the key here is to look at the patient's needs as well as the doctor's needs and to keep that paramount, which -- I assume that is the purpose. And there's a million patients that are waiting for this procedure -- not a million patients need the procedure, but it's -- the data that I've have seen have shown it to be very effective, where other treatments fail.

DR. GARBER: Thank you very much.

All right, we're about to move into -- Perry, was there anything else? Perry, are you done with your -- oh, well -- yeah, okay, he's done.

And then we'll -- the next will be a presentation from Medtronic given by Dr. Bakay -- is that the correct pronunciation? -- and Dr.

Montgomery.

And I need to ask every speaker, and especially in the public session, to declare your name, your affiliation, and any conflict of interest or any potential financial or other interests you would have in the topic today.

MR. OWENS: Good morning. I'm Cliff Owens. I'm vice president and general manager of the Global Movement Disorder Business for Medtronic, and I'd like to introduce our two speakers.

This morning, these two physicians are going to outline the clinical evidence of Activa brain-stimulation therapy for the treatment of advanced levodopa response of Parkinson's disease and essential tremor to provide you with the evidence to support approval of a national Medicare coverage policy.

Activa is not a cure for either one of these diseases. It is a therapy that significantly extends the time when patients are able to function more normally. Activa is reversible so that when -- if and when a cure is found, the devices can be removed and the cure implemented. Additionally, unlike the ablative therapies it replaces, the Activa system is adjustable, allowing dosing that

best fits the level of disease in each patient.

The two physicians that we have here today are experts in the area of neurological movement disorders. Dr. Erwin Montgomery is the head of the Movement Disorders Section, the director of the American Parkinson's disease Advanced Center for Research, medical director, American Parkinson's disease Association Information Referral Center, the co-director of the Center for Functional and Restorative Neurosurgery, and a member of the Department of Neurology and Neurosciences at the Lerner Research Institute of the Cleveland Clinic Foundation in Cleveland, Ohio. He has numerous medical achievements, and, for the second time, I will not list those today.

Dr. Roy Bakay is professor and vice chairman of the Department of Neurological Surgery at Rush Presbyterian St. Luke's Medical Center at the Chicago at the Chicago Institute of Neurosurgery and Neuroresearch. Dr. Bakay is a member of the AANS and CNS Joint Washington Committee, on the Editorial Board of Neurosurgery, and also has a very long list of medical achievements.

Both Dr. Montgomery and Dr. Bakay are active members of the brain-stimulation implant

teams in their respective institutions. They are experts in the procedure and will answer all of the medical questions.

The Activa Parkinson's disease clinical trials will be reviewed, including 18 centers from around the world. The database contains over 32,000 data points. And, therefore, in the audience, we have several Medtronic people that may, from time to time, help answer specific questions.

Thank you, and now I'd like to introduce Dr. Montgomery.

DR. MONTGOMERY: Good morning. It's a pleasure to be here to talk to the panel.

And as Cliff mentioned, I am a neurologist at the Cleveland Clinic Foundation. And in terms of any conflict of interest, we do receive research grant support from Medtronic for some of our research activities there at the Cleveland Clinic Foundation.

And what I'm going to do is talk to you a little bit about some of the clinical data regarding Activa Therapy, both for Parkinson's disease, as well as for a essential tremor. I'm going to be sharing with you some data from thalamic stimulation as well as stimulation the globus pallidus internal

segment, as well as the substantiam or subthalamic nucleus.

And so this -- drawings here demonstrates the various devices. You can see, for example, the actual implanted leads here that are implanted into the various targets. And you can see from this volunteer, a gentleman who has the leads placed in the subthalamic nucleus bilaterally. You can see the leads are then in place. They exit through a small burricle and attach to an extension wire that then is tunneled subcutaneously to the impulse generator that's implanted underneath the skin over the chest, just beneath the clavicle. So this kind of demonstrates the usual procedures, then, for a subthalamic nucleus as well as globus pallidus. Thalamic surgery would typically be unilateral.

Here you can see a drawing of the impulse generator, the Selectra. This is the programming module that the physician can use to program the device. And here, you can see a external magnet that the patient or the physician can use to turn the stimulator on or off.

And so I'm going to describe some of the results of the some of the trials. And I'll think that as you -- as you see some of these results, I

think you will agree that this truly is a breakthrough technology in the very definition of the word "breakthrough." I think you will see that, really, the comparison, in terms of the effectiveness of this therapy, is not against the medication, and it does represent, really, a totally different approach, a totally new approach, for the treatment of patients with Parkinson's disease and essential tremor.

And as I go through some of the subsequent clinical data, I want to emphasize to you that the -- the types of patients that were enrolled in these studies. These were end-stage patients, in terms of the Parkinson's disease study for subthalamic nucleus and globus pallidus. These were patients in whom nothing worked, in terms of medication. These were patients who were treated by some of the world's leaders in movement disorders, and they gave up, virtually, on these patients.

So, for these patients, the issue was not medication versus surgery. For these patients, it was surgery or nothing, in terms of their efficacy. And so I can -- I am sure you can appreciate that these were difficult end-stage patients, and I think it's very important to keep, then, the results of

the clinical trial in that context.

And, as you'll see, then, that the average on time was increased by -- can we go back? -- the average on time was increased by nearly six hours for patients with subthalamic nucleus and the globus pallidus stimulation. This represents nearly a doubling of the "on" times that these patients have. This means that, now, that the patient is functional, can get up, care for themselves, feed themselves, participate in activities of daily living.

You can also see that the dyskinetic "on" time -- that is, these patients are now mobile. They can get up. They can move around. Their tremor is improved -- their rate of kinesia, slowness of movements -- improve. But before, they were plagued by severe involuntary movement, severe dyskinesia. And, for many of these patients, it is often a difficult choice of being immobile, or being mobile, but too mobile, so mobile that they actually couldn't function. And, many times, the dyskinesia is more disabling than the Parkinsonian symptoms, as well.

And you can see, then, that the amount of dyskinesia was substantially decreased by these

therapies and that this is not just a few patients getting dramatically better, but a large percentage -- over 87 percent have had significant improvements in their motor examination, the neurological examinations, at that 12 months when the medications were -- when they were fasted from the medication.

And actually now most of the Medicare local carriers do cover this therapy, but I submit to you that a national policy is, indeed, needed.

And this shows a very important measure. This is the "on" time, without dyskinesia. Again, this is when patients are mobile. They can get up, care for themselves, do things that they need to do, and, at the same time, not plagued by the severe involuntary movements. And you can see here that 74 percent of the younger Parkinson's patients have gotten significant improvement, in terms of their "on" time. And 53 percent of even older Parkinson's patients got significantly better. So better than half of these patients, now, were much more functional following deep-brain stimulation.

This shows the "on" time with dyskinesia. And this shows that over 71 percent of these patients -- these younger Parkinson's patients -- had a significant reduction in the dyskinesia. So

they're still mobile, but not plagued by these severe involuntary movements. And when you look at the older population, again, 46 -- nearly half of these patients -- had significant reduction in their dyskinesia -- again, quite a remarkable benefit.

This shows the UPDRS score, which is the motor examination, and it -- a more objective assessment of the patient's responsiveness to therapy. And again, I think you can see the data is quite overwhelming. The degree of improvement and the number of patients that improved with this therapy, whether they're younger than 65 or older than 65 -- again, very dramatic improvement. So I think that, again, for these patients in whom medication is not -- no longer an option, this truly does represent breakthrough therapy.

I'm going to show you some additional data. This relates to unilateral thalamic stimulation for the treatment of tremor both in patients with Parkinson's disease and essential tremor. And again, you'll see that the results have been quite dramatic. The average tremor-rating score went from a 3.3 to 0.78.

Let me put that in context for you. This is based on the tremor rating scale where zero is no

tremor, and four is such severe tremor that the person can't even perform the task. So, for example, we will ask them to bring their finger to their nose. Actually, we don't have them bring it to their nose, because we're afraid they're going to poke their eye, so we have them bring it to their chin. And these patients are so severe that they can't even bring their finger to the tip of their nose or to the tip of their chin. And that would give them a ratings score of four. So you can see, then, many of these patients have clearly approximated that severe tremor.

And then look at the dramatic reduction in their tremor. One is just intermittent tremor, so quite dramatic improvement. And we see the same degree of improvement, then, with patients with essential tremor.

And then this goes -- this shows your form, the improvement in tremor for Parkinson's patients versus essential-tremor patients -- and again, divided into the two age groups -- less than 65 years of age and equal to 65 or older -- again, quite dramatic improvement. And again, these assessments were made a year after the implantation of the device.

So those are just some of my brief introduction to some of the clinical data. And at this point, I'll turn the podium over to Dr. Bakay.

DR. BAKAY: Thank you. I'm privileged to be here and present some of this to you.

The appropriate candidates for bilateral STN or GPi deep-brain stimulation are patients who have advanced symptoms but yet have retained some ability to respond to levodopa therapy. I think that's the central element of this.

Evaluation of these patients require an expert, like Dr. Montgomery, to make sure that they've had adequate trials of medication and that they are then refractory and no longer responsive, in most cases, to the adequate control of medication. And then they have to be surgical candidates, in the sense that they have to be able to tolerate the stresses of surgery. And obviously, those are candidates that one would evaluate separately. And then the final aspect is approved with the appropriate labeling.

The appropriate candidates for the unilateral thalamic stimulation are patients who have disabling tremor from essential tremor or from Parkinson's disease. The tremor must be found to be

functionally disabling. The tremor is then also refractory to pharmacological therapies. And, again, the patients have to be able to undergo surgical intervention -- and, again, consistent with approved labeling.

In order to perform surgery, you have to have the appropriate equipment, appropriate staff. The appropriate equipment, of course, is -- requires the stereotactic frame, the ability to image the patient, the ability to understand and know the electrophysiology to be able to ensure that the lead is placed properly.

The neurosurgeons have undergone a great number of years of training within the neurosurgery residency period. All of the trainees are exposed to stereotactic and functional training to a variety of degrees. There are, in fact, fellowships for additional training thereafter.

I think, as I mentioned before, the real essential element to any team approach to this is that one has to have a neurologist involved -- a neurologist involved who can be able to evaluate these patients and make sure that they have had appropriate medical therapy before they undergo the surgical therapy.

The neuro physiologist is an elective member. Some of the neurologists and neurosurgeons have more than sufficient neurophysiological understanding to be able to conduct these. Neuro psychiatrists are obviously very helpful, in terms of evaluating patients, preoperatively. We don't want to be performing patients who are demented patients who have underlying depression and other things that need to be treated before they undergo any type of surgical intervention.

In terms of training, there's a variety of training available, both through Medtronic and through professional organizations. You can see the number of things there that Medtronic offers, and they can expand upon that, if necessary.

In terms of professional organizations, we have courses, and we just finished a series of courses at each of the meetings, nationally, as well as individual courses such as the one sponsored by the Cleveland Clinic just recently in South Carolina.

So, in summary, then, we feel that there is compelling evidence of the clinical effectiveness for bilateral STN or bilateral GPi stimulation that there is, in fact, also more than adequate evidence

for a unilateral thalamic stimulation for tremor.

There is evidence that the Medicare patient population will be one that will be very positively affected by this treatment. And the thing to insist upon is that there is adequate ability to perform this surgery satisfactorily.

Thank you.

MS. ATKINSON: Now I would like to introduce Joan Vatz, from BlueCross and BlueShield.

DR. VATZ: The report I'm presenting this morning was reviewed by the Blue Cross and --

DR. GARBER: All right. Joan?

DR. ZENDLE: Alan, if there is a question of the speakers, do you want to do that first?

DR. GARBER: Yes, brief questions just for clarification, because I think If it's relating to the discussion, we'd like to defer it. I hope that both of you will be staying through at least the morning's part of the proceeding, because your presentation touches upon, very directly, a number of areas of questions that I think the panel will want to explore further.

But are there any questions of clarification, at this point? Okay, thank you. Sorry, Joan.

DR. VATZ: The report I'm presenting this morning was reviewed by the BlueCross and BlueShield Association Medical Advisory Panel in December of 2001 and was published as a technology assessment in January 2002. It represents the work of the Technology Evaluation Center, one of several AHRQ designated evidence practice centers in the United States.

My own background is in the practice of internal medicine, including the care of some Parkinson's disease patients. And I have a fellowship training in technology assessment.

Parkinson's disease is a chronic, progressive, neurodegenerative disease that usually appears after the age of 40. Its incidence increases with advancing age until it reaches a peak at about the age of 75. And it currently affects about a million and a half people in the United States.

The disease impairs a person's ability to control movement. The first symptoms are usually a tremor, trembling, or shaking on one side of the body. Patients also can experience constantly contracted-muscle rigidity, substantially slower movements, bradykinesia, and inability to initiate

movement, akinesia, abnormal involuntary movement, dyskinesia, and impaired balance and coordination. These symptoms are related to dopamine deficiency and usually respond to levodopa.

Although pharmacologic treatment with levodopa and adjunctive drugs can restore smooth motor movements up to five to ten years in most patients, medication effectiveness diminishes with time. Furthermore, and this is important, this -- the degenerative nature of the disease is not confined solely to the dopaminergic system. The brain may be affected more globally as the disease progresses. Thus, symptoms that are not responsive to levodopa may develop. These symptoms include dementia, motor symptoms that affect speech and swallowing, sleep disturbances, depression.

The diagnosis of early Parkinson's disease may be difficult. Traditionally, the presence of two of the three classic symptoms of Parkinson's disease provided the basis of diagnosis: resting tremor, rigidity, or bradykinesia. However, clinical diagnosis based upon these criteria alone were found to be incorrect in 25 percent of cases in the London-Britain Bank study in 1992. MRI studies support this misdiagnosis rate. (Inaudible)

reported in 1998 that 25 percent of patients with Parkinsonian symptoms have an atypical disorder, such as multiple-system apathy or progressive supranuclear palsy, rather than idiopathic Parkinson's disease. Thus, the diagnosis of Parkinson's disease has shifted somewhat, and these are predictors that are more often used now.

Specialists in nucleus disorders distinguish at least two major subtypes of Parkinson's disease -- a tremor-dominant subtype and a rigid, akinetic subtype. It is generally accepted that patients with unilateral tremor-dominant disease seem to progress less rapidly, have less cognizant dysfunction, and respond differently to anti-Parkinsonian medication than patients with the rigid, akinetic subtype of disease. Patients with the rigid, akinetic subtype have symptoms that are more symmetrical and experience more dystonia, more axonal involvement, and early dyskinesia.

Everyone learns in medical school this definition of Parkinson's disease. The corpus striatum is part of the basal ganglia. It's made up of two cellular masses, these nucleuses. These masses arise as a single body in early development and then separate as the brain develops. They

remain continuous centrally -- how can you make the slide go back; okay, thank you -- and are connected directly by a number of slender gray bridges across the internal capsule, which you can see in this diagram.

Parkinson's disease, then, is the degeneration of the monoaminergic neurons in the substantia nigra. These neurons project neuritic processes through the striatum shown here that -- to modulate activities of the extrapyramidal system to two critical functions: the production of dopamine and the regulation of its release from these terminals. Certain motor symptoms of Parkinson's disease appear when this modulation is lost, as these cells gradually die.

In fact, however, Parkinson's disease is also a complex global disease involving the progressive death of many selected groups of neurons throughout the brain. Here are some of them, as listed in Lang & Lozano's 1998 review. This is sections of the brain showing where this area's nuclei lie. Here are some more of them that are affected in Parkinson's disease.

It's important to have a solid sense of the neuroanatomic complexity of Parkinson's disease.

I'd also like to spend a few minutes to call your attention to the definitions in Table A of the BlueCross and BlueShield assessment. This has terms of -- definitions and terms used in studies of Parkinson's disease. For practitioners unfamiliar with the study of Parkinson's disease, these terms may seem rather arcane.

The first one, "off" period, refers to a variety of conditions ranging from brief periods of relative immobility and loss of dexterity, due to a temporary loss of medication effect, to the condition that occurs after prolonged withdrawal of anti-Parkinsonian medication. Advancing Parkinson's disease is characterized, then, by a lengthening of these "off" periods, or periods of relative immobility and loss of dexterity that occur gradually as the dose of levodopa wears off.

The "off" condition is an operational definition in which the term "off" ignores what true "off" may be in the patient's life or that there may be several different types of "off" for any given patient. This term was developed as a working definition in 1992 to promote standardization and comparability in Parkinson's disease studies.

Now it usually refers to a standard

practically defined "off" condition created for purposes of a study by withdrawal of medication for 12 hours. In practice, this is often simply the state the patient is in in the morning before taking the first dose of levodopa or anti-Parkinsonian medication. There are a few other terms where "off" is a condition that both the patient and the physician agree is as severe as the symptoms ever become.

"On" periods are periods of maximum mobility and dexterity when medication is working. There is a "best on" condition.

And there are motor fluctuations, which are abrupt, unpredictable "off" periods -- that is, periods of relative immobility and lost dexterity that may last from a minute to an hour and are followed by an equally abrupt return of medication effectiveness, or an "on" period. Such on/off fluctuations may occur frequently throughout the day or even during an hour and are not temporally related to levodopa intake. Motor fluctuations occur in approximately 50 percent of patients after five years of levodopa therapy, and, at this stage, usually affect patients for less than 25 percent of their waking hours.

Dyskinesia is -- consists of abnormal involuntary movements. These are highly variable movements. With time, they become a major cause of disability in Parkinson's disease. One type of dyskinesia seen early in the course of treatment consists of abnormal movements, usually at the head, neck, torso, or respiratory muscles. And these occur when the effective medication is at its peak. Many patients, particularly early in the course of the illness, are unaware of the presence of these movements, and they are reversible and rapidly disappear if levodopa is withdrawn or if the dosage reduced. There are other kinds of dyskinesias that develop in later Parkinson's disease.

Dystonia -- some patients develop painful "off-period" dystonia, which is an increase of muscle tone resulting in fixed, abnormal postures and sometimes abnormal movements.

There are a number of tools used for the evaluation of Parkinson's disease -- these two slides show them -- and it's important to have a good sense of these terms before going on, because they appear over and over in the studies people will be talking about today.

The UPDRS is perhaps the most widely used

measure. It was published in 1987 and consists of a comprehensive inventory of symptoms and signs of Parkinson's disease, which I divided into sections pertaining to mood and mentation, activities of daily living, motor function, muscle rigidity, speech, and gait. Scores range from zero, which is normal, to 176, which is the worst possible. Patients are questioned and examined in both the off-medication state, usually before the first morning dose, and then the on-medication state, which is usually defined as the best test scores measured during the day when the patient is taking the levodopa.

This slide shows a sample of one of the items for postural stability. A patient is subjected to a strong, sudden posterior displacement produced by a pull on the shoulders. While standing erect with the eyes open and feet slightly apart, the patient is prepared, and then the examiner observes which of these responses the patient has.

The Schwab and England scale is a measure designed exclusively to evaluate performance of activities of daily living, and the scoring is the reverse of the UPDRS, with 100 indicating normal, and zero, the worst possible.

The Hoehn and Yahr staging system is one of the oldest measures used in Parkinson's disease. It consists of six major stages and emphasizes mobility.

There are some other subjective patient-generated ways of looking at Parkinson's disease. All in all, I think you can tell, evaluation of treatment for Parkinson's disease is extremely labor intensive. Symptom severity changes from week to week, from day to day, from minute to minute. So the purpose of these is to obtain some more data points.

First, there are diaries. These are from the Deep Brain Study Group Multicenter Trial, the diary evaluations that we used in that. Another method used is home video recordings at frequent intervals, which is more labor intensive, but has a few advantages over the diaries, in that the videos can be examined blindly and rated by an objective examiner permitting blinding of the examiner and some standardization of the rating, and then they allow a more -- a larger number of data points to be examined, which may screen for some of the noise generated by fluctuations in the disease. These have been used in some of the cellular

transplantation studies of Parkinson's disease.

Treatment options for advanced disease consist of medication or surgical options shown in this slide. But, as noted, medication becomes less effective with time. And the unilateral procedures offer limited benefits for patients with bilateral disease; thus, the interest in bilateral deep-brain stimulation.

The two targets under study are relatively small structures -- the subthalamic nucleus, which you can barely see here, but this shows how it all relates to the extrapyramidal system. It's a small ovoid nucleus with a volume 150 to 200 cubic millimeters in humans. It lies a little bit lateral to the substantia nigra and is bounded externally by the internal capsule. The globus pallidus interna is a larger structure -- banana shaped with a volume of about 500 cubic millimeters in humans and is bounded by the internal capsule, caudally, and by the optic tract, ventrally. Both of these structures are anatomically complex in that both contain sensory motor regions, and both contain complete thalamatotopic organization.

How does deep-brain stimulation work? No one knows for sure, but here are some of the

theories that have been proposed in the literature.

And now we'll get to the body of the assessment. We used three search methods to generate our reference list. And these study-selection criteria -- here are a few more of them.

Since we were interested in bilateral stimulation, mainly because Parkinson's disease is a bilateral disease, studies in which outcomes for unilateral procedures were analyzed together, where those of bilateral were excluded from the assessment.

Also, some other studies examine single outcomes, such as the affect of deep-brain stimulation on voice production. These studies, which focused on a single outcome, are required to use such highly specialized measures, were also excluded as beyond the scope of the assessment.

Finally, there is concern over the potential adverse affects of bilateral procedures upon neuropsychiatric function. Since it is the bilaterality of the procedure, rather than the choice of targets, that is the primary concern in these studies, outcomes of studies of either nucleus were considered together in the case of neuropsychological evaluations.

This assessment was formulated with these -- were structured with these -- with this formulation, these four segments.

Patient indications. These were the patient indications that were provided in most of the -- in all, I would say, of the studies that we used. If you look in the assessment, on pages 24 through 29, in the fourth column -- it's a very busy table, but it shows some of the patient characteristics, as well as inclusion and exclusion criteria used.

Despite the use of these indications, it's still a little hard to determine, in this entire body of literature, exactly who these patients are. Some studies exclude patients with abnormal MRIs, while others have patient cohorts with nearly a 50-percent rate of MRI abnormality. Some present extensive baseline staging information, while others do not.

With advanced age and exclusion factor -- it's never stated, really, as such -- patients as old as 74 have been studied. However, most patients are younger than 65 at the time of implantation in the studies that we included in this.

The technologies to be compared. To

examine this procedure, the ideal comparison would be best medical management from a specialized movement disorder. Another possible comparison would be with the accepted unilateral surgical treatment, a unilateral pallidotomy. Most trials, however, compared deep-brain stimulation in the "off" and "on" condition with the patient's preoperative baseline control. Whether this baseline condition always consisted of careful best-medical management as a protocol cannot be determined from most of these trials.

These are the health outcomes, the benefits to be expected from deep-brain stimulation. They lie in the realm of motor improvement and medication reduction. These four key benefits were reported in most of the trials.

Adverse effects consists of these conditions related to the procedures, to the device, and to stimulation.

Because of the experience with bilateral ablative procedures, which carry a high risk of postoperative cognitive dysfunction, the question arises, does bilateral deep-brain stimulation pose a similar risk? So we looked at studies that examine neuropsychiatric function, as well.

The specific -- the assessment poses this specific question.

And then the analysis of the evidence. We found that there was no large prospective randomized study with long-term follow-up of bilateral deep-brain stimulation. In no published studies are patients randomized prospectively to treatment on -- that compared deep-brain stimulation with best medical management. There is one small pilot study that is prospectively randomized, and that compares subthalamic nucleus and globus pallidus interna targets. And that study is by Dr. Burchiel in 1998.

The reported patient numbers -- the reporting of patient numbers is complicated by the possibilities that outcomes from some patients may have been published in more than one of the reports included in this assessment, so we tried to get around it by the following logic.

If you look at Table 1, in the fourth column, you can see the number of patients listed in each study. If none of the -- if no patients described in any of the single-center trials were included also in the deep-brain study-group trial, then we have outcomes in the published literature for 287 patients. However, many of the

investigators in the deep-brain study-group trial have also published single-center trials. And if you assume that the deep-brain study-group published outcomes from all or some of the same patients in the single-center trials, then the outcome -- we'd have outcomes for as few as 186 patients.

Since we couldn't tell from the literature which was which, we chose to go with this conservative number of 186 patients. And in the discussion of the outcomes, we assumed that all the deep-brain study-group investigators have published outcomes on the same patients in both single-center trials and the multicenter trial. That leaves 186 patients for the subthalamic nucleus studies, and 53, as a conservative figure, for the globus pallidus interna. It may be more than that, but we don't know for sure.

Randomization is a design issue. Only one -- only the one pilot study provides a true randomization. The multicenter trial randomization consists of including all patients who underwent implantation. And then in the postoperative examination sequence, patients were randomized in terms of the crossover examination of whether they were examined with stimulation "on" first or

stimulation "off" first.

Outcomes. Things like home diaries provide some questions about validation and standardization. Still, despite this, the published evidence is quite compelling, both because of the numbers of effectively treated patients and because of the consistency of the patients -- the consistency of the findings across the study and the magnitude of the clinical improvement.

There are, in the assessment, 14 published trials describing motor outcomes among 186 patients, with follow-up at six months for 151 one of these, and, for at least 12 months for 116 patients.

There are nine published trials examining the globus pallidus interna as a target with motor outcomes among 53 patients and follow-up from three months to as long as 30 months. Ten trials examine neuropsychiatric function after treatment in at least 139 patients.

The key outcomes in these trials are these four, which we have looked at before. For the sake of time, however, we can focus, as we look at these outcomes, upon the outcomes reported in the deep-brain study-group report, which was published in the New England Journal in September of 2001.

Motor improvement in the "off" condition -- that's the condition when the patient is relatively immobile, in terms of the study design, but it would be the condition the patient has during the day when their doses of levodopa wear off. Mean UPDRS scores improved by 51 percent with the subthalamic nucleus stimulation, and by 35 percent among the globus pallidus interna patients.

Similar motor improvement was reported in all 14 studies of the -- using the subthalamic nucleus as a target, and in eight of the nine studies of the globus pallidus interna.

Activities of daily living improved also in the "off" condition by 44 percent and 38 percent. Percentage of time with good mobility increased dramatically. The daily levodopa equivalent dosage was reduced among patients with subthalamic nucleus stimulation, but this was not possible among patients with -- when the globus pallidus interna was the target.

Complications are similar to those known for thalamic stimulation. Persistent neurologic deficit was reported in the deep-brain study-group among seven of the 143 patients, or 2.8 percent. Infections occurred in four of the 143 patients,

seizures in four of the 143 patients, lead migration in five, and stimulation-induced dyskinesia requiring parameter adjustment in five. These were the major complications.

These can be compared -- if you look in the assessment at Table 4, on page 45 -- with complications reported after a ablative pallidal surgery. Intracranial hemorrhage was reported in four studies of pallidotomy with incidents of 1.5 to 12 percent. Postoperative confusion occurred in four to ten percent of patients. And cognitive difficulty occurred in up to 12.5 percent of patients.

Observations from patients with hemiparkinsonism suggest that the right and left basal ganglia have distinctly different roles in the mediation of verbal and visual spatial abilities. For example, patients with right hemiparkinsonism -- that is, disease that involves the left basal ganglia -- these patients show greater deficits in verbal abilities than patients with right hemiparkinsonism.

Conversely, patients with left hemiparkinsonism -- with right hemiparkinsonism -- no, I get the left and right mixed up. I'm sorry.

Patients with left hemiparkinsonism -- that is, disease that involves the right basal ganglia -- tend to have more profound visual spatial defects.

Laterality of a surgically-created lesion has been found to be a significant determinant of neuropsychological sequelae after unilateral pallidotomy. Thus, some patients who were generally pleased with the motor outcomes of their pallidotomy were often restricted, then, in their ability to function properly at work or in social settings by behavioral changes and losses in verbal fluency.

Thus, the question of whether bilateral deep-brain stimulation poses a similar risk is an important one, and there are ten studies reviewed in this assessment. They're presented on pages 65 through 69. They evaluate 139 patients. Nearly all of these studies find some degree of loss in verbal learning and/or language function.

In one of the most-recently publication -- most recent publications by Allegret and Colleagues -- it's the first article in your literature volume -- memory, visuospatial, and frontal function were evaluated in 15 patients three months after bilateral implantation. It was found that, in this group, bilateral subthalamic nucleus deep-brain

stimulation produced a mixture of beneficial changes, including moderate improvement in prefrontal task and obsessive-compulsive traits, and detrimental changes, which consisted of moderate deterioration of verbal memory. The authors conclude that since, in general, all surgical procedures for Parkinson's disease involving the left or both hemispheres appear to negatively affect verbal memory, and since all involved nuclei are related to memory processes, some change in learning ability after these procedures as -- is to be expected. So there is consensus, in general, among these studies that the risk, while present, is minimal.

And these are the criteria -- the BlueCross and BlueShield Association Technology Evaluation Criteria. We created a discussion base that follows, sort of, the order I've given you of this data. And -- based upon these criteria -- and based upon the evidence, bilateral deep-brain stimulation of the subthalamic nucleus or the globus pallidus interna for patients with advanced disease was voted to meet these TEC criteria in December.

DR. GARBER: Thank you, Joan. Any questions of clarification? Okay.

MS. ATKINSON: I would like to introduce Celia -- Dr. Celia Witten from FDA.

DR. WITTEN: I'd like to thank you for inviting me to come and present the FDA's review process for these devices and what we based our review decision on. I'm Dr. Witten, and I'm the division director of the division in the Center for Devices that's in charge of pre-market review of, among other things, neurological devices.

There's a number of different pathways by which a product can be approved, and I've listed them here on this slide. The one that's, by far, the most common is the first one, the pre-market notification, or so-called 510(k) pathway. And FDA approves probably upwards of 4,000 products a year for that pathway. But that isn't a pathway for fairly novel products, like this one, which went through the pre-market approval pathway.

So other than just saying that our criteria for approving products in these different categories are different, I'm going to move on and focus on the criteria for approval and the process for approval of pre-market approval applications.

So I guess I actually went through the -- slipped by the first slide, which was an outline of

my talk. So I'll just mention that I'm going to give you a little bit of regulatory background, and then I'm going to talk about the history of these submissions, and then go on and give a little bit of detail primarily from the summary of safety and effectiveness that you have in your package that was provided you in advance.

So, to continue with the regulatory background, a product like this would be studied under investigational device exemption, which is the mechanism by which FDA regulates clinical studies that are performed on unapproved devices to support a marketing application. And they can support a marketing application of any one of those types of devices.

We only are -- have authority over studies performed in the United States. So studies performed outside of the United States, or sites that perform studies outside the United States, aren't under the IDE regulations.

And the IDE is -- under an IDE, a sponsor will perform a study to get a systematic collection of safety and effectiveness data. And, in this case, this was considered a significant-risk study, so it's approved by the FDA and approved by the

Institutional Review Board of the centers that conduct those studies.

For a PMA, a sponsor needs to show that there's reasonable assurance of safety and effectiveness. And I'm going to give you the regulatory definition of safety and effectiveness in a subsequent slide. And those are defined on the basis of risk and benefit to the patient and clinically significant results to the patient population for which -- for the target patient population.

In a PMA application, we generally would see clinical data from an IDE study, although not a hundred percent of the time, and a summary of safety and effectiveness with proposed labeling for the product. And the product is then reviewed by the ODE division, which, in this case, is the division that I'm the director of. And we get other reviews from other Center for Device offices, as needed.

In this case, this product, for both the original application and the subsequent application, were reviewed by an FDA advisory panel, as well.

We have a regulatory definition of "valid scientific evidence," and there's a hierarchy of valid scientific evidence of which the highest rank

is well-controlled investigations. And this hierarchy of evidence includes partially controlled studies, trials without matched controls, well-documented case histories, and reports of significant human experience.

And, as Dr. Vatz has already pointed out, there aren't well-controlled investigations or -- in the sense of randomized studies against another treatment, but the evidence that we looked at for this -- these marketing applications certainly fit within the spectrum of valid scientific evidence, as our definition gives us.

The definition of "safety" is, "Reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health under conditions of use outweigh any probable risks."

And what I want to just point out here and also under the definition for "effectiveness" is the "under conditions of use" part, and that is, we don't approve just the device. It's the device plus the particular use that it's -- that -- for which that device is intended.

And so in this -- that's why there were two separate approvals, the original approval for

the tremor indication, followed by the indication for the Parkinson's indication, because of our regulatory scheme that the product is the product plus what it's supposed to be used for.

Our definition of "effectiveness," "Reasonable assurance that a device is effective when, in a significant portion of the target population, the use of the device for its intended uses and conditions of use will provide clinically significant results."

So, again, it's -- it's specific use. It's the device plus its use, and we are directed to look at clinically significant results in that target population.

Moving on to the history of this, as has already been mentioned, the original approval was for unilateral thalamic stimulation for tremor suppression. And there was a supplement approved early this calendar year for bilateral globus pallidus or subthalamic nucleus stimulation for Parkinson's symptoms. In each case, the application was reviewed by an FDA Advisory Panel, who recommend approval for the product.

The indications for use -- I'm not going to read them. They're in your package. But it's

for suppression of tremor in the upper extremity. And, as has been mentioned, it's for unilateral tremor suppression -- unilateral use.

The tremor study was for patients with Parkinson's disease or central tremor that was disabling and not adequately controlled by medications.

I'm just going to mention here that the mean age in this study in the U.S. was 67 years, and in Europe was 63 years.

Effectiveness. There were -- the effectiveness was based on a rating scale from zero to four for tremor in Parkinson's based on one of the questions in the UPDRS, and for the central tremor based on one of the questions in the tremor rating scale. The questions are slightly different, but the rating scale in both cases are on a zero-to-four basis. And the analysis was based on comparing equivalent and individual patients with stimulation "on" compared to stimulation "off," and with stimulation "on" compared to the patient's pre-implant state.

The Parkinson's disease indication for use is for bilateral stimulation as adjunctive therapy in reducing some of the symptoms of advance

levodopa-responsive Parkinson's disease not adequately controlled with medication.

I'm -- I put this slide in -- this is the precautions from the label and from our summary of safety and effectiveness for this product. And the point I want to make here is just that I know the question is going to come up about what a precaution means compared to a contraindication, and we have in here uses -- specific populations that -- we don't have specific safety and effectiveness information for these populations. But this is not a contraindication. And so this is just information that -- for example, in the case of over the age of 75 years, that we don't have specific information in the population, but it is not a contraindication in the FDA labeling for that product.

The study supporting this indication was in 160 patients. There's a slight error on this slide. There were 18 centers, four in the U.S., and 14 outside of the U.S. But some of these were in Canada and Australia. So there were 18 centers, four in the U.S., and 14 outside the U.S.

The inclusion criteria is ages 30 to 75. They were patients with idiopathic Parkinson's with a good levodopa response, as has already been

mentioned previously. That's one of the factors that is felt to predict an ability to respond with this device. And patients had to have a certain criteria in terms of severity of their Parkinson's disease, as characterized in the last three bullets on this slide.

Sixty-six-point-nine percent of the patients were males. The mean age of disease onset was 43.9 years, and the mean age at the time of implantation was 58 years, with a range of 32 to 75 years.

The parameters -- there were a number of parameters assessed in the study. The ones that we focused on in our assessment for safety and effectiveness were the UPDRS -- motor portion of the UPDRS, the patient diaries regarding the "on" and "off" states in dyskinesias, and also, of course, safety.

And some of the safety events that are most concerning -- and these are on the basis of the number of patients with each event. So 12 out of 160 patients had intracranial hemorrhage, 17 had device-related infection, 16 had paresis/asthenia, and 13 had hemiplegia or hemiparesis. And some of , a patient with intracranial hemorrhage and

hemiplegia would have been counted in both categories.

What we looked at for total motor exam scores. The symptoms of Parkinson's disease improved for 56 out of 117 patients while on mediation, and improved for 102 out of 117 patients while off medication.

And I'll just mention again that this "off" medication, as Dr. Vatz has already said, is not the "off" state -- it's not the "off" state mentioned in motor fluctuation. It's practically defined "off," where the patient is off medication for a certain period of time prior to their assessment.

Now, what we looked at more closely is -- we wanted to look at what patients improved -- what was the definition of improvement for an individual patient. So what this histogram shows you is the number of patients who had no change. And no change, in this case, was defined as no change of -- or a change of less than five points. So for a patient to get into the right-hand side or the white bars of this histogram, which shows improvement, they had to have improved by at least five points on the total motor exam score of the UPDRS.

And in this case, we're looking at the patients who improved in the total motor exam "off" mediation by target. And, again, this is "off" as defined as having been off their medications overnight.

And the comparisons made here and in the prior slide are between the preimplantation state and the 12-month state.

Looking at the diary results, the duration of the "on" time was increased by an average of 6.7 hours and 6.1 hours in the GPi and STN patients, respectfully. And the duration of "on" time with dyskinesia is decreased in both groups, as well.

Here, again, we've got a histogram that shows the magnitude of the improvement in the patients in these two groups. And, on the right, you see the definition of "improvement" is "improved by at least an hour." And the histogram shows -- breaks down a little bit further. Patients who improved between one and four hours is a plus-one category, and for the -- plus-two category means the patient improved between four and seven hours, in terms of their amount of "on" time; and then the plus-three category, between seven and ten hours. So that -- there's an ability to see a little bit

more the amount of benefit that the individual patients received from this treatment.

And this slide shows you the absolute change in "on" time with dyskinesias, by target. I'm not going to read it. But, again, there's a breakdown to show how much individual patients improved on this parameter.

So I'll stop here and ask if there's any questions. Thank you.

DR. GARBER: Okay, thank you.

And now we have the scheduled public comments.

MS. ATKINSON: Our first speaker is Dr. David Charles.

DR. CHARLES: I'd like to thank the Chair and members of the Advisory Committee.

My name is David Charles, and I'm on the faculty of Vanderbilt University in Nashville, Tennessee.

My research in the area of deep-brain stimulation is supported by private not-for-profit foundations, Medtronic, Incorporated, and the governments of both France and the United States. At Vanderbilt University, I'm director of the Neurology Residency Program and also director the

Movement Disorders Clinic. My practice is primarily focused in movement disorders and in the area of the application of deep-brain stimulation for the treatment of tremor and Parkinson's disease.

I've worked with patients with Parkinson's disease and the application of this therapy since 1994, and served as a Fulbright Scholar in France, studying this therapy.

Today, I rise on behalf of the American Academy of Neurology, speaking on behalf of this organization, which is the largest organization representing neurologists in the United States, over 15,000 members, representing both the members and our patients.

I will not review here the data regarding DBS, but will give you the position statement of the American Academy of Neurology. And that is that we encourage this advisory panel, in the strongest possible terms, to recommend a national policy coverage decision for the application of deep-brain stimulation for the treatment of tremor and Parkinson's disease.

Deep-brain stimulation for the treatment of Parkinson's disease, particularly stimulation of the subthalamic nucleus, represent the most

significant advance in the treatment of Parkinson's disease in almost 30 years. The American Academy of Neurology is fortunate to have had many of its members participate in this research, both in the United States and in Europe.

While it's not in the purview of this committee to consider, the American Academy of Neurology would also like to state for the record that, for Medicare patients to actually have access to this therapy there must be an appropriate reimbursement policy that covers every aspect of this therapy, including the preoperative evaluation, the implantation of the device, and the follow up for the patients through the remainder of their care.

I thank the committee for the opportunity to speak.

DR. GARBER: Thank you.

MS. ATKINSON: Our next speaker is the Jante's, Ellen and Dale.

MS. JANTE: Thank you for your time today. I don't have the credentials of all the other speakers that you've heard so far, but Dale has -- you could you stand up for a second? -- Dale has Parkinson's, and we're very personally involved, and

we wanted you to hear from someone who was.

For most of us today, this is a pretty normal day. Maybe you don't do what you're doing today every day, but you're living a normal life. This day, for Dale and I, is monumental, and for thousands of other patients like Dale.

We aren't going to preach to you today about Parkinson's disease. You already know it. You've seen patients, I hope, who have it. And we would like to tell you, though, what an average day is like. First of all, there are no average days, but just a glimpse.

The possibility that subthalamic deep-brain stimulation surgery could offer Dale and others -- excuse me -- a semi-normal life would be a miracle. Dale is 56 years old now -- not unlike the age of several of you, I'm sure, in the room -- and was diagnosed with Parkinson's when he was 43. His symptoms started with a tremor. No problem. We can deal with that. Unless you're an accountant, and you need to use the computer to do your work.

The month he was diagnosed, he lost his job and all healthcare insurance. Fortunately, he qualified for high-risk insurance, which costs -- which had $1,000 deductibles and $300-a-month

payments. Since he had no job, we used our savings to pay for that insurance so that he would have coverage.

Fortunately, since then, he's been covered by Medicare, and he's on total disability, he has been for a few years. We had to appeal for five years to qualify for Medicare, even though he could not work. And he's also covered by the Veterans Administration, because he's a Vietnam veteran.

The tremors led to stiffness and difficulty walking. His ability to think and speak is diminished because of this disease and the 43 pills he takes every single day. No one knows what the results or the interaction of all these medications is to other parts of his body. The 14 prescriptions that are refilled every months cause major side effects. In fact, three years ago, Dale suffered congestive heart failure as a result of the medication, Mirapex.

Fortunately, his heart has recovered. And that's the good news. And his cardiologist feels that his heart would be fine if he underwent brain surgery.

Since entering this room this morning at 7:30 a.m., Dale came in "on" -- you may not have

realized that he had Parkinson's. Since then, he's been "on" -- just took his medication, so he'll remain "on" for quite some time now before those medications kick in.

His day revolves around his medications. It takes him one and a half hours in the morning to be able walk after taking the medication. Until then, he can only sit in his chair. He takes pills every three to four hours. Approximately one hour before a dose, he freezes up -- cannot move at all and cannot function for at least another hour.

Even when his medications work, he stumbles, falls, has slurred speech, he drools, and has involuntary movements. There are no good ways -- no good days anymore, just good minutes. He can't plan for anything, because he may not be able to move or communicate. Last Saturday night, he crawled to bed on his hands and knees just to get to bed, because he could no longer walk. There's no wheelchair in our house. Dale knows that once that wheelchair comes in the house, he'll never get out.

We're asking you today to put that wheelchair time on for him and others like him. But, in spite of this, he considers himself lucky, because his friends with Parkinson's who are the

same age as him are in wheelchairs.

I'm going to skip part of this, because I know I'm running out of time, right?

He researched the effectiveness of pallidotomy and thalamotomy and decided that was not for us. Two -- the lesions would cause too much permanent damage. But he began studying the Emory study on DBS.

We debated whether he could have the surgery to correct his tremors so that he could eat without dropping his food, work on a computer, address himself unaided, and feel more relaxed in public. And then the stiffness set in.

Just helping the tremor isn't enough. Just imagine how badly you would have to feel to ask to have two holes drilled in your brain. How bad would you have to be?

So I want to know what the price we can pay for the value of living a normal life. Surely you know someone with Parkinson's. Everyone does. I would hope that you would act for a better quality of life for those people.

We live in Wisconsin. Medicare does not cover this surgery in Wisconsin. We're covered by WPS. So we believe that we could cut his -- and

obviously other people could, too -- cut their medication by 40 to 80 percent, and he could improve that much.

We wondered what we could do to impress you today. First of all, we came at our own expense. We are thrilled to be here today with professionals who have -- who can make the decision to help us. Then we asked for signatures. And, on May 17th, we began gathering signatures. There's almost 3,000 signatures of people that have Parkinson's, and caregivers, and other people we know that are concerned about this.

So we are asking you to make difference for thousands and thousands of patients, like Dale, who are awaiting this much-needed treatment. We ask you to help those who can't help themselves.

Dale is thinking positively, believing that, if you had a relative with Parkinson's, you would not hesitate to give them a better chance for life. So we encourage you to give Medicare your blessing, to nationally cover DBS surgery.

We thank you very much for your attention to this issue today.

DR. GARBER: Thank you.

MS. ATKINSON: And our last speaker, Dr.

Frederick Lenz.

DR. GARBER: Okay, I'm going to ask the sense of the panel. Several of you, I know, are interested in carrying out the deliberations fairly rapidly, if it's possible to do so. Would you like to take a short break now? Or no break, and just people go out when they want and move into deliberations? What is the sense of the panel?

PANELISTS: No break.

DR. GARBER: No break, okay.

So we will now move into open panel deliberations. And, at this point, I'd like to just go around the room, since everyone is present, and have each panelist briefly introduce themselves.

Joan Samuelson?

MS. SAMUELSON: Thank you. I am the president of the Parkinson's Action Network, which is a nationwide advocacy group on behalf of the Parkinson's community.

I've had Parkinson's for 16 years. I am one of the lucky ones who was able to walk into the room when I -- when the medication is working, but I just wanted to mention that. And, for those of you who don't live closely with Parkinson's, you got a good summary of it from Mrs. Jante -- and I thank

you for that -- but I wanted to reiterate that.

When I wake up in the morning, it takes me an hour to be able to move. And I apologize for being late, but it took a little longer this morning.

That's the foundation from which I approach the approval of this device, and I'm privileged to be a part of the panel.

Thank you.

DR. GARBER: Thank you.

Dr. Satya-Murti?

DR. SATYA-MURTI: I am Satya-Murti. I am a neurologist with an academic background. I still practice neurology at a defined location. And I'm also a carrier medical director for Medicare for three Midwest states, and I've been doing that for several years.

And my questions, eventually, would, of course, be more technical, and they would cover neurologic aspects and some coverage-issue questions.

And we are one of the -- probably not one -- I was the first one to write a Medicare coverage policy for this condition, if that calls for any dubious distinction.

Thank you.

DR. LITVAN: I'm Irene Litvan. I'm a neurologist. I'm the chief of the Cognitive Neuropharmacology Unit. I'm affiliated with John Hopkins, and I have participated with Dr. Hallad in the review of the surgery indications in Parkinson's disease as a task force for the American Academy of Neurology, and I've been following all these issues for several years.

Thank you for inviting me.

DR. WEINER: I'm Dr. William Weiner. I'm a professor of neurology and chair of the Department of Neurology at the University of Maryland School of Medicine, and the director of the Maryland Parkinson's disease and Related Movement Disorder Center. I've been involved in taking care of Parkinson's patients and performing clinical research in Parkinson's disease since 1968-69, and have a longstanding interest in these issues.

DR. FOLLETT: I'm Ken FOLLETT, professor of neurosurgery at the University of Iowa Hospitals and at the Iowa City Veterans Administration Medical Center.

I am the principal investigator of the VA/NIH collaborative trial, which will compare best-

medical therapy to deep-brain stimulation and will compare deep-brain stimulation of the subthalamic nucleus to globus pallidus.

This trial has just begun enrollment within the last four weeks or so. We plan on enrolling a total of 326 patients into this trial. It is a prospective randomized control trial. Patient enrollment is going to take about two years, and it will involve a minimum two-year follow-up for each patient. So we're looking about four years down the road, five years down the road, before we have results from the trial, but we anticipate that this study will answer many of the questions that have been raised in discussions related to the effectiveness of deep-brain stimulation and whether one site for deep-brain stimulation might be superior to the other.

DR. HOLOHAN: My name is Tom Holohan. I'm chief of patient care services for the Veterans Health Administration. With respect to Medicare, I'm the chair of the Drugs, Biologics, and Therapeutics Panel, and, like Dr. Garber, am a member of the Medicare Coverage Advisory Committee Executive Committee.

MS. GREENBERGER: I'm Phyllis Greenberger,

president and CEO of the Society for Women's Health Research. I'm the consumer representative, and my mother has Parkinson's.

DR. BURCHIEL: I'm Kim Burchiel. I am chairman of neurological surgery at Oregon Health and Science University. I've been doing movement-disorder research for most of my career. I sit on the Diagnostic Imaging Panel of MCAC, and have been seconded to this panel for this particular issue, and it's a pleasure to be here.

DR. SIGSBEE: My name is Bruce Sigsbee. I'm a panel member. I'm a neurologist practicing in Massachusetts in private practice, but also a member of -- at the Department of Neurology of Brighams and Women Medical Center. Perhaps 40 percent of my practice has to do with movement disorders.

DR. RATHMELL: I'm Jim Rathmell. I'm an associate professor of anesthesiology, and I specialize in pain medicine at the University of Vermont. I'm chair of the American Society of Anesthesiologists Committee on Pain Medicine, and I'm a standing member of the committee.

DR. ZENDLE: My name is Les Zendle. I'm the associate medical director of the Southern California Permanente Medical Group. I am an

internist and a geriatrician. I was on the BlueCross/BlueShield Association Medical Advisory Panel from '93 until '99, and I've been associated Medicare coverage determination panels since '99.

DR. MC BRYDE: Angus McBryde. I'm a professor of orthopedics at South Carolina. And I come at this kind of as prevention of hip fracture, interested in gait examination in kiddies, as well as things of this sort, and I'm glad to be here.

DR. PHURROUGH: And I'm Steve Phurrough. I'm the CMS liaison for the committee.

DR. GARBER: Alan Garber. I -- of course, I am the chair of this panel. I'm a -- an internist -- general internist with the Department of Veterans Affairs, and a professor of medicine at Stanford, where I also direct the Center for Health Policy and Sanford Primary Care and Outcomes Research.

Now, our last public speaker has arrived, so I hope you won't mind if we go a little bit out of sequence here and give him a chance to speak.

MS. ATKINSON: Dr. Frederick Lenz?

DR. LENZ: I would like to start off by just saying a few words about the history behind this. I guess the three facts that have led to the situation where surgery is again being considered an

important part of the treatment of movement disorders is: The neurologist's recognition that they had come to the end of what they could do in patients with advanced Parkinson's disease or tremor or dystonia.

The second thing was the three sites that you keep hearing about are all understood physiologically much better than they ever were in the past, and it's now clear that there's increased activity in each of these conditions for which surgery is now being performed.

And so, of course, this -- the demonstration that there was increased activity in these areas led to surgery which involved lesioning or destroying these areas in order to decrease the amount of activity. And the -- and then, of course, that was unpalatable to the neurologists and the surgeons and everyone else, and so it was a great step forward when the French group demonstrated that high-frequency stimulation had the same effect as lesioning.

So the targets that we're talking about are all part of one circuit and the increased activity in all of them. And, for reasons that are not entirely clear -- or there is a different

spectrum of effectiveness in the treatment of each of these different conditions. And, although the exact indications for one or another site in a particular condition is not fully worked out, there are a number of double-blind trials of different sites in the treatment of, particularly, Parkinson's disease.

So the indications for choosing these sites are, in the case of the thalamic target, the -- the best recognized indications are Parkinsonian and central tremor. The other kinds of tremor, such as intention tremor or rubril tremors are still an area where the indications are not entirely clear.

The -- in the case of GPi stimulation, which again is one of these basal nuclei which are all interconnected, the indications are advanced Parkinson's disease or dystonia.

And then the third target, the subthalamic nucleus, the only target at -- the only accepted indication, at present -- although there are a number of others being proposed, the only accepted is advanced Parkinson's disease.

In carrying out these procedures, it's -- some very basic things. It's essential to have a movement-disorder neurologist who can evaluate the

patients to decide what the diagnosis is, in fact, and the -- and also whether maximal medical therapy has been employed in the case of a particulate individual. And the third thing is to adjust the stimulators, because, particularly in the case of Parkinson's disease, the medications and stimulators are adjusted simultaneously.

So the -- those are the -- what I would view as the indications for these procedures. And the other thing to say is that it's -- different centers vary as far as carrying out these procedures. Probably in the best of all possible worlds, you would have a physiologist or a -- or someone who is expert in electrophysiology to locate the electrodes appropriately.

You have to understand, the size of these targets is measured in terms of a small number of millimeters between the -- the mentalis intermedius, which is the thalamic target, is about a tenth of an inch in depth at about the level that we implant. And the -- and subthalamic nucleus is sort of a small, bean-sized structure. So it's essential to get -- to confirm your target physiologically somehow.

And the -- I think those are probably the

main technical requirements.

There are a number of programs that have been devised to optimize the radiologic targeting that's carried out so that you get the best possible radiologic fix on the nucleus that we're after and then confirm that physiologically.

Contraindications for these procedures --

DR. GARBER: Dr. Lenz? Dr. Lenz, pardon me, but you've used up your time. I'm sure that we will have questions for you shortly, though.

MS. ATKINSON: And also, one more thing. Could you please disclose, for the record, whether you have any financial involvement.

DR. LENZ: No.

MS. ATKINSON: Thank you.

DR. GARBER: Okay, thank you.

So, now we will return to the open panel deliberations. And before we -- I thought that what we would do is go through the questions. But this would also be a good time to direct any questions that panel members have toward this morning's speakers. And please keep in mind that our main concern, of course, is to get information that will help us address the questions that CMS has put before us.

Dr. Litvan and then Dr. Weiner?

DR. LITVAN: The question I have is something that we discussed in our conference call and is, How much of training is necessary for a neurosurgeon to be able to become good at practicing deep-brain stimulation in these areas? And is there any curve of learning? And is there any requirement as -- as many number of procedures made before someone is trained? And what is the rate of complications that would be allowed as to still continue to have the risk-benefit ratio?

I was looking at the -- some of the presentations -- some of the publications, and it seems like some centers do have much more complications and do seem not to have good, beneficial effects on the patients; whereas, there are others that are excellent, you know, in terms -- so would you give us some sense?

DR. BAKAY: Well, that's a very complex issue. Certainly, neurosurgeons in their training are exposed to stereotactics. That's part of a sub-specialization within the subspecialty of neurosurgery. Many people have taken on that as an -- a particular area of expertise.

As to -- as to the number of complications

and that sort of thing, that is -- that is part of the learning curve. In fact, all the data you saw is part of the learning curve. You know, most of these centers are starting up to do these procedures. So I would anticipate that most of the complication rates, early on, are going to be much more -- higher than those that will occur later on, as one refines the procedure.

Certain things as lead fractures, we were initially instructed to place the lead down in the cervical region. Well, that turns out to be a very bad place to put it, because lead fractures are extremely common. Lead connections now are placed in -- on the cranial surface. Lead erosions from the rather large connector now are less common, as there is a smaller connector available. So there are improvements, both in the technology and in the -- in the surgical techniques.

Obviously, the rate of complication should be relatively low, in terms of severe complications, those of hemiparesis, blindness, et cetera. And how low? Probably in the -- somewhere in the three to four percent range, I would anticipate. In terms of expertise, that may even be -- they may be able to generate that even lower.

Certain complications such as infections are very difficult to control despite the use of perioperative antibiotics. It is said there's more bacteria in your mouth than there are people in the world, so it's a constant struggle to keep infections down and out, but that is something that we can improve technically as we do the operation more frequently.

In terms of who should be doing the procedure, I don't think this should be done by somebody does not have experience with it in some form or another, whether they got it through their training program or whether they acquire it through some of the continuing education. But that's my personal opinion.

Does that answer that satisfactorily? It was series of question you answered, and I hope I covered most of it.

DR. LITVAN: Yeah. Is there a minimum amount of time that you think it is necessary? Of course, this is your opinion, but as -- in practicing --

DR. BAKAY: I think there's two things. One is training. The other is the center. I think a multi-disciplinary approach is really quite

essential to these.

These are very complicated patients. The neurosurgeon is basically a technician in this aspect. The patient is under the control of a neurologist, in general, and very much should be, because of the complexity of the medical treatment. And it's obviously the -- that when the medical treatment fails, when there are marked fluctuations in the patients' responsiveness to medication, that you then become a surgical candidate. It's not something that you do up front.

So medicine is the first aspect. And most of these patients should be treated by an expert in movement disorders, or at least screened by an expert in movement disorders, and not simply sent to a neurosurgeon or somebody decides that they want to have their surgery based on the fact that they were told they had this disease and now want to have the surgery. So some sort of screening element, I think, is necessary, in terms of expertise.

And in terms of the surgery, obviously, the more experience, the better. That's the case in all things. But you have to start someplace, and I think there are a number of ways in which someone who is not currently involved with this can get up

to speed relatively quickly, and that involves courses, but also visitation to centers that do the procedure and then -- and then some potential assistance while they are starting to do their first initial procedures. It can be achieved by a variety of ways.

DR. BURCHIEL: I'd like to respond to that.

DR. GARBER: Dr. Weiner?

DR. BURCHIEL: Could I respond to that?

DR. GARBER: Go ahead.

DR. BURCHIEL: I mean, I think you've put your finger on the Achilles heel of a lot of surgical training, that this is a new procedure, which, I think, officially neurosurgery says is part of the training. But I think Roy knows, and every other neurosurgeon knows, here, that there are people that are -- that are dedicated to this in certain programs. And other programs don't have anybody like this. And so there's a wide variety of training in -- within a neurosurgical residency program.

And without becoming too prescriptive, I think that the decision down the road is going to have to incorporate some sort of criteria of who can

and can't do this. I mean, is it a weekend course? Is it a -- one visit, watching somebody from the corner? Or is it a year? Nobody knows. I do think those things tend to sort themselves out.

But we -- neurosurgery does not have official fellowships in any area, this included. There are unofficial fellowships out there, where someone can go to Dr. Bakay or a number -- Dr. Lenz or other folks -- and learn this procedure very well. But then you might have to ask those folks, What does it require?

There's -- there clearly is a learning curve, and I would submit it's probably not a weekend. It's something longer than that.

But I -- it would almost seem more reasonable for this to be a local carrier decision that the -- that CMS shouldn't be too prescriptive about this, and that -- should leave that to the carriers to make those decisions.

DR. GARBER: Dr. Satya-Murti?

DR. SATYA-MURTI: Yeah, thank you. These are pertinent questions. I had them on my eye -- in my own mind, as well. When I first wrote the policy, I did, with some trepidation and hesitation, say that there ought to be some experience built

into it. It's often difficult to separate coverage from science. Try as we may, the two go hand in hand, and we find it more and more so in Medicare.

So one other criterion, besides the number of surgeries or years in experience, would be how much time does the prospective movement-disorder specialist and neurosurgeon spend on performing this procedure? Drawing strength from cardiac surgery and previous data collected on centers of excellence and volume versus outcomes, I -- as a carrier, I do have some proposals that, if CMS finds it applicable, we can apply to this, but I also endorse that there ought to be some numbers put to this, even though it's only a lattice on which we can build later.

And I'd like to propose that at least 50 percent of the surgeon or movement-disorder neurologists, their time ought to be expended in running such a clinic and performing surgery. So that's just a number I would like to start with, if, at all, we address that.

DR. GARBER: Yeah, let's follow up on that when we get -- go through the questions. I think that will be very pertinent.

Dr. Weiner?

DR. WEINER: I'd like to just sort of follow up on this question about the training. I mean, it does get to be very difficult to know who should do it or who should do it, but as a neurologist, I mean, if a neurosurgeon is trained in stereotactic procedures and is doing biopsies, for example, is this sort of just considered -- you're moving to a slightly different "gadget", so to speak, in the OR? You know, in other words, if you're a stereotactic surgeon -- you know, for example, would a weekend course be sufficient, as opposed to if you've never done a stereotactic procedure?

DR. BURCHIEL: Well, I would say absolutely not. This is -- this is not just a flavor or stereotactics. This is a whole different thing. And others may have other opinions, but I do think this is not simply something you can pick up in a few hours.

DR. BAKAY: No, I think -- I think this is a very complicated and difficult issue. The -- if you have some familiarity with stereotactics, you're much better off than somebody who's never done one, but you still have to understand the anatomy and the electrophysiology of this area. You have to

understand what the stimulator will do and will not do. You have to understand, What do you do when you get into problems? And these things take time to experience.

And, you know, there are centers that have been doing this for quite a long time, and I don't think these centers could lay down absolute criteria for what you should do. It is an area of difficulty. There is -- as Kim said, there is no certification as a stereotactic or functional neurosurgeon.

DR. GARBER: Dr. Montgomery? Or Dr. Lenz, did you want to comment?

DR. MONTGOMERY: Yeah, I think the questions that you're asking about the experience and training of the neurosurgeon has to be broadened to include the experience and training of the team. And as Dr. Bakay mentioned, it's not just the neurosurgeon and that the neurologist/neurophysiologist is very much involved in the deliberations in the operating room and making the judgments as to where to place the lead and assessing the effects of stimulation the operating room. So you have to look at the combined team, and I think that, you know, there can be

balances and tradeoffs, depending on the various members of the team. So --

My only other concern, though, is that, in establishing any policy, I would urge flexibility. I -- this field is evolving rapidly, and we're very much involved in developing techniques and methodologies that will greatly reduce the required sophistication of the users. We're developing expert systems for doing the electrophysiology. And so my hope is that very soon we'll see that the technical requirements, in terms of the level of sophistication, will get considerably less.

And my concern is any policy that's not flexible, that's carved into stone, really could wind up hurting this field rather than helping.

DR. LENZ: I think that depending on the means used to localize the target, you're going to need training in one of a -- one of a number of fields, particularly radiology, because the techniques that are used to light up the -- and recognize on an MR scan -- the targets, are not necessarily straightforward. Electrophysiology is a complete field on its own, and if you're using a microelectrode, that's something that can only be learned over probably a year or so.

And the other thing is it's a totally different mindset from the way most neurosurgeons do intracranial procedures, which is -- in this kind of surgery, you're trying to identify the physiologic target. What most intracranial neurosurgeons do is just try to stay away from areas where they know they can get into trouble. And so it's a totally different mindset, and I think it takes a significant amount of training.

And I would echo again what Dr. Montgomery said, which is that the neurologist -- it's absolutely key that they be a very experienced movement-disorder neurologist making these decisions about indications for surgery.

DR. GARBER: Okay, thank you.

Les Zendle, I think you were next.

DR. ZENDLE: Actually, he was before me.

DR. GARBER: Oh. Jim?

DR. RATHMELL: To extend on that, now you have someone who has gone out and gotten experience, come into your center, and the team has come to your center and spent some time with you. You feel that they're on the verge of launching this. Now they go out, and they're trying to decide this unilateral versus the different -- you know, unilateral,

bilateral versus the various target sites. It appears as though the data is yet to come. How are they going to make those decisions? How do you recommend them, aside from recommendations from the manufacturer themselves that have been advised by experts, like yourself? Is that the way you would expect new folks approaching this field to apply it?

DR. BAKAY: Well, in terms of approaching the target, there is -- you know, obviously if the tremor is the predominant symptom, many -- in essential tremor, there is only one target, so you don't have concern. In terms of -- in terms of Parkinson's disease others would say that the subthalamic nucleus does tremor just as well as VIM, Why don't you just put in there, and it will take care of the other problems that'll occur later? So there are difference of opinion and difference of philosophy.

I think it's like having multiple medications. You don't have to say that that medication is good only for this particular type of Parkinson patient or that particular type of Parkinson's patient. There is overlap, and these are really treating symptoms of the disease.

And so the fact that we don't know what is

the better site really isn't, to me, a major question. You have two good sites that are -- that are equally efficacious.

I think we need to leave it to the surgical team to decide how they're going to do the surgery, whether they're going to do it in one stroke or two. I think there are a number of cases where a unilateral stimulator is all that you really need, especially in patients with asymmetrical disease. And I think there are times when we will go out to do a bilateral procedure and see how the patient does after the first one. If there is some confusion, if you've lost your examination during that time, you stop and come back another day, or you may plan ahead of time that this is a patient who is not going to tolerate sitting, and do it in two stages. I think that ought to be left to the discretion of the surgeon. That'll be worked out over time.

And there's not the data available to hit that as a -- as a -- you know, like a pill that you could take a Q4 hours or whether you should take it Q8. This will -- this is something that'll work out in time.

You have two good targets. You have the

ability to use either one. And I think some of these studies that are undergoing will help us, but may not -- you know, the final answer may not come for many years as to which is the better site and why. I mean, we may find that you can decrease the medication off the STN, but there may be more cognitive side effects with that procedure. So which is the better one? You know, that'll have to be sorted out, and it'll take time to do that, but these will sort out with time.

The fact is that you've got two effective treatments, and that they ought to go forward.

DR. GARBER: Okay, Dr. Montgomery.

DR. MONTGOMERY: I don't want you to have the impression that we're -- that the decision is a roll of the dice. That's absolutely not true. I think most movement disorders -- neurologists, there's a very strong and emerging consensus in terms of the approach to answering these questions. So this is not willie-nillie a roll of the dice, and it's not high -- you know, idiosyncratic to each movement-disorder neurologist. There is an emerging and strong consensus. First.

The second point is -- is that both therapies, in terms of STN and GPi, are effective.

They are both remarkably effective, and they are both associated with a paucity of significant complications. The perioperative morbidity rate is very reasonable for both procedures.

I do not think at this point in time that we do a patient any disservice by selecting GPi versus STN, or selecting STN versus GPi. I think there's a growing consensus that thalamic stimulation is really not -- not a good target, and that's because we all recognize that, while it is very effective for tremor, it is not effective for bradykinesia, it's not effective for postural stability.

And even though a patient may initially present with tremor, over the course of the next few years, he's going to develop all of the other symptoms, so I -- you know, and if you just look at the number of centers, there are very few of the major centers that are implanting thalamic stimulators anymore.

And our own decision, our choice of doing STN versus GPi is really a technical issue. We tend to favor the subthalamic nucleus, because we can get to it much easier. It requires fewer penetrations from the microelectrode to find the optimal target

than does GPi.

And then I think in terms of the prospective study -- what I'd look to the prospective study to help answer is not relative to the efficacy of STN versus GPi, but to help sort out some of the cognitive issues and complication issues. But even still that, those are fairly minimal considerations when you contrast with the degree of improvement that these -- either of these therapies make.

So I hope you don't take away the impression that this is something that's arbitrary, that, you know, we make the decision by plucking something out of thing air, and that we need long-term studies to answer that question. There is already a very strong consensus in the community.

DR. GARBER: Dr. Holohan?

DR. HOLOHAN: Yeah, I think we're getting away from the original question, which was a question about criteria for experience and training.

In terms of the location of the placement of the electrodes, if there were evidence favoring one location versus the other, it would unethical for the VA to carry out the trial that, in fact, we're carrying out, where patients are randomized.

I don't know that -- how far, Alan, you want to get into the issue of training and experience. There obviously are probably a majority opinion, I would presume, in this group. But the question we really asked is whether we think Medicare should impose criteria for centers that do this. I don't think we have to develop them. I would submit that it's probably difficult, and perhaps inappropriate.

In that light, I'd like to ask Dr. Follett, who is probably the one most responsible for the institution of the VA trial, to talk about the criteria that the VA used to select the six centers, not with respect to their research abilities, but with respect to their abilities to accomplish the surgical procedure that's part of the collaborative study. Would you be willing to elaborate on that a little bit?

DR. FOLLETT: I'll give it a try. I'd like to point out -- I want to make one comment to emphasize what Dr. Montgomery mentioned. The fact that we have multiple targets isn't bad. It doesn't mean we don't understand the therapies -- we don't know whether one works, the other doesn't work. The fact that we have multiple targets, I think, is

good. It gives us an element of flexibility with these therapies and lets this multi-disciplinary team try to tailor the treatment to the needs of each individual patient.

The purpose, I think, of the collaborative trial, in particular, isn't necessarily to find out whether one site is really better than the other, but I think it's to find out which site is best for a certain set of symptoms, which site is best for a certain subset of patients. So we want to try to address this issue of tailoring the therapy to the patient, that Dr. Rathmell raised. For the time being, we have to rely upon the expertise of a multi-disciplinary team to evaluate the patient and decide which of these surgical options is best suited to the needs of that patient.

DR. RATHMELL: And I just -- I want to emphasize -- what I'm hearing from you is, if this goes out -- my question was, to the general practitioner, how does he decide? How does he or she decide, okay? And it sounds like what I'm hearing from you, it doesn't matter. It's okay to choose on an individual basis. It's okay, in your view, for each center to decide on their own amongst these therapies individually. They're all equally

acceptable at this point in time.

DR. FOLLETT: At this point, each of these therapies -- and we're talking about STN versus GPi implants -- they seem to be comparable. But -- and I wouldn't say that it's up to the general practitioner to select which to use. I think it's up to the multi-disciplinary team at each center to decide which therapy would be best in their hands, in their center for that patient.

DR. GARBER: Well, maybe -- you know, we're getting a little off track here. This is --

DR. BAKAY: (Inaudible.)

DR. GARBER: -- something that we need to discuss. No, no. I'll let you finish. I just wanted to say, in terms of the structure of the discussion, this is getting very deeply into something that we have in order as we go through the questions. We're getting a little off track here. This is something we need to ask you, but I just want to say, in terms of the structure of the discussion, this is getting very deeply into something that we have to, in order as we go through the question, what should be the target, we will need, since this isn't a role of the dice, we will need some information on how to decide, and you will

be allowed to do that. I would like to continue discussion in the context of hearing Dr. FOLLETT's point and then if there are questions directly related to the discussion here that should not occur in the discussion context of going through the questions later, then you can ask them now, and to clarify things like what should be the target, or what we need to do implants in globus pallidus and subthalamic nucleus.

DR. FOLLETT: Let me come back and say that in neurosurgery, we have as an organization, we have never prescribed a number in order to show competencies, and I think the same holds for the technique of deep brain stimulation. There probably isn't a minimum number of procedures to become competent, it depends on his training and so on. For the VA study, in order to maintain at least, to try to maintain a standard uniform quality, we did decide that an eligible surgeon in order to meet our selective criteria, should have performed a minimum of 15 to 20 implants, and I don't recall the exact number. There should have been a minimum number of pallidotomies and a minimum number of implants.

But, in addition to the basic mechanics of handling the wires during surgery, there are the

added skills that Dr. Bakay mentioned, and Dr. Montgomery, in terms of identifying the proper targets, and that begins to draw up on the need for intraoperative electrophysiology testing, whether it's microelectric recording, micro stimulation or macro stimulation.

So overall, we felt that at least a minimum of something on the order of 15 or 20 implants should have been performed by the surgeon in order to meet the minimum criteria to participate in the study.

DR. GARBER: Okay --

DR. HOLOHAN: There were other criteria, beyond the neurosurgeon, though, in terms of your reference to the multi-disciplinary group.

DR. FOLLETT: That's correct. In addition to having a neurosurgeon who was technically qualified to perform the surgery, we did require that the centers have a multi-disciplinary team, which include a neurologist, who has training and expertise in the management of movement disorders, and also a center that has a neuropsychologist with some expertise in the evaluation and management of patients have movement disorders.

DR. GARBER: Okay, thank you. Les Zendle

and then Bruce Sigsbee, and then we'll move on.

DR. ZENDLE: Yeah, I don't want to address the neurosurgical technical implantation issues, but I was very impressed with Dr. Bharchua's letter that we got prior to the meeting, and I think it's in the packet, that talked about the correct diagnosis and the fact that there -- some patients without Parkinson's disease -- or a correct diagnosis, or patients with early Parkinson's disease that are being encouraged by neurosurgeons to have this procedures, and a lot of advertising on television, et cetera. I wonder if you could address that issue, because I think that -- I would hope we would be concerned that the right patients are getting this procedure.

DR. MONTGOMERY: The issue comes, in terms of the differential diagnosis of Parkinsonism. And when we talk about Parkinsonism, we're talking about a spectrum of disorders ranging from idiopathic Parkinson's disease, which accounts for about 24 percent of all patients with Parkinsonism, and then there are the atypicals, supra nuclear palsy, multi-systems atrophy, cerebellar atrophy.

Quite -- occasionally the differential diagnosis can be very, very difficult, but there are

now fairly well-established criteria that we use to minimize the risk of inclusion of somebody who doesn't have idiopathic Parkinson's disease. The United Kingdom Brain Bank study, which did a postmortem controlled study. And looking back at the types of symptoms that could distinguish an atypical Parkinsonism from someone with Parkinson's disease idiopathic is pretty well worked out.

And I think most movement-disorders neurologists are well aware of those criteria. We specifically look for things like limitation of volition eye gaze. We specifically look for symptoms of profound dysautonomia. We look for ataxia. We look for upgoing toes, hyperreflexia.

So I think that the criteria are fairly robust, in terms of making that sort of distinction. And most neurologists, and certainly most movement-disorders neurologists, are familiar with those sorts of criteria.

Is that going to exclude the occasional patient with atypical Parkinsonism getting the surgery? No. I think that's an inherent risk in this procedure, but I think it is going to be very, very minimal.

DR. WEINER: Well, I think, if it's okay

to follow up on the question about patient selection, I had wanted to ask both you and Dr. Bakay, in terms of your presentations about how you phrase the degree of levodopa responsiveness or what was the role of that. And the reason -- the reason was is that it was my understanding that patients who have the correct diagnosis and who have levodopa-responsive Parkinson's disease still have to have some period of time in which they respond to their medication. And I think you both referred to the fact that levodopa didn't work anymore, so that -- you might get people confused -- a general neurologist, for example, confused with an atypical Parkinson patient who never responds to the medication, and never did, or who responded minimally and then lost that. So I wonder if you could clarify the levodopa responsiveness.

DR. MONTGOMERY: Certainly. Well, going back to the autopsy control study by Lees and Hughes in the United Kingdom, and they did a retrospective analysis and found that those patients who had autopsy-proven idiopathic Parkinson's disease by the presence of Lewy bodies, and when they went back and looked at the records, 97 percent of those individuals had some history of response to

levodopa. When they went back and looked at the patients with atypical Parkinsonism, only about a quarter ever had any kind of reference in the past medical record of any response to levodopa. So I think the notion of having had some levodopa responsiveness is a good criteria for helping assess a surgical candidacy.

Now, but, as Dr. Weiner points out, what does it mean to have a levodopa response? And, at the same time, it sounds almost paradoxical that we're requiring them to be refractory to levodopa and yet at the same time insisting that they have a levodopa response. What we -- what we look for in selecting patients is some history that the patient had some improvement of their symptoms, even if it was brief, even if it was complicated by side effects, but some history of ring responsiveness.

Perhaps the biggest issue that we have is making sure they've had an adequate trial. You know, 600 milligrams of levodopa per day is not an adequate trial of levodopa.

So I think that we're very confident that if a person has had some improvement in their Parkinson's symptoms, even if it's only brief, even if it's associated with significant side effects,

like dyskinesia, that that still constitutes fairly strong criteria for a reasonable conclusion that the patient has idiopathic Parkinson's disease.

DR. WEINER: But even beyond the diagnostic question that you're elucidating, what about the -- in selecting the patient, do they still have to have some time period of levodopa responsiveness in order to be a surgical candidate?

DR. MONTGOMERY: Yeah, I agree. And I don't think that we've taken any patient to the operating room who has not had some improvement. But, again, the question is what degree of improvement.

I can tell you, when we looked at the pallidotomy study, in working with Dr. Lang and Dr. Lozano, we went back, and that had -- that was a very positive outcome -- we went back and actually looked at the degree of improvement on the UPDRS scores following an administration of levodopa, and there was no correlation with the postoperative outcome. So you cannot use the magnitude of levodopa response as a criteria for admitting patients to surgery. And if you did, you would really just exclude a large number of patients who need the surgery. So that -- you know, that's a bit

problematic.

DR. BAKAY: I think one of the problems is that -- is that you get into some of the side effects of the medication. And so if you're just strictly using the UPDRS score, you can get into problems.

But what you want to see is the fluctuation, and I think that's really critical -- is how good are they on their best "on," and then compare that to how bad they are on the "off" score. And there should be a clear, significant difference and -- in the eyes of the neurologist who's doing that evaluation.

And, again, I'd emphasize that that's a role for a neurologist and not a neurosurgeon, that these things are sometimes rather subtle, and sometimes they're very dramatic. And the people that I see that are going to improve the most are the ones that have the marked fluctuations, and those are marked fluctuations in terms of responses going from frozen, to being able, to do something, to being extremely dyskinetic. And somewhere in there -- and exactly what percentage improvement, it's very difficult to say. I mean, we tried to include that in several of our NIH studies, and it's

extremely difficult to make a set criteria of how much improvement you want to see. It's more of a gestalten. As you get more experience, it becomes clearer and clearer, but it is a gestalten.

DR. MONTGOMERY: Just one more -- maybe a point of humility? I mean, we've heard of point of orders, but this is a point of humility.

Actually, we really don't know, because almost every study has required levodopa responsiveness to get into the study. Nobody's done surgery on patients who have demonstrated no levodopa responsiveness, and so we don't know that, you know, that we're not excluding patients who could otherwise benefit.

DR. BAKAY: That's not true. There have been patients that have -- and you just don't find them in the literature. Those patients are frequently not reported. Dr. Lozano's got a few. The Emory group's got a few.

Atypical patients have been done, in terms of trying to evaluate these patients, but they have not been part of a formal study. But the -- almost all of us that have experience with atypicals realize that they do not very well.

DR. GARBER: Okay, Dr. Sigsbee?

DR. SIGSBEE: Just one comment. The whole area of neurodegenerative disease in the nervous system is a moving target. As we look at the underlying molecular biology, we're recognizing that certain disorders can have a wide spectrum of possible clinical manifestations. But I think it's still -- you can fairly reliably, through the criteria discussed, identify people who have idiopathic Parkinson's, whether a combination of levodopa responsiveness and other clinical criteria.

I do have, I think, another question here, as I would like to ask about the Medtronic marketing for this device. And I would like to preface that by saying that I'm aware of one device that's used to help control seizures that is very heavily marketed. I know a neurologist who is not an epileptologist who went away to a weekend course, was certified and is -- now does it in conjunction with a surgeon -- tends to look at a failure of a few anticonvulsants and then go to this particular procedure, as opposed to epilepsy centers where they look at a whole spectrum of surgical interventions.

There's another device that I know of that's recently been available to physicians for treatment of abdominal aortic aneurysms. That

device manufacturer works closely with the local credentials committee, sets criteria for training of the individuals, has somebody who is expert in it come and observe a number of surgeries, and, only after that individual is signed off, can those individuals do it independently, both in terms of case selection and the technical expertise.

And with those comments in mind, I wonder if Medtronic would comment on their marketing plan.

MR. OWENS: I'd be happy to. I think you will find that we are very consistent with what the movement-disorder neurologist and neurosurgeons have said. Our approach is to have centers that are well trained that are supported by a team that has a clear understanding of this. We do not want to have any patient implanted without the best possibility of good outcomes.

We are marketing this from the standpoint of making sure that patients are informed about the opportunity, but we are telling them to see, first, their neurologist, then move on to the movement-disorder neurologist, and then move to the neurosurgeon. We are -- have already planned and continue to have a number of courses where we make sure that people that are interested in doing this

procedure are very well trained and then have the opportunity to follow up with key people, and a number of people who are on the panel here, to make sure that they understand this clearly and to know exactly what to do.

I do think that the comments about having a -- the team approach are critical, that you need to have a movement-disorder neurologist there that is clearly aware of what to do. We also very much focus on the procedure itself. We have devices for microelectrode recording that are available. We have surgical-planning techniques and software that are available that we encourage, if they will improve the determination of the proper anatomical and functional targets that those are specifically used by those surgeons. And in almost every case, they are.

We are taking a very focused approach to functional stereotactic neurosurgeons. There will be stereotactic neurosurgeons, obviously, that will do this. And I think that either Dr. Bakay or Montgomery or Dr. Follett made a comment about the rapid evolution of this technology as we move forward. And that is one of the things that we are working very closely with and trying to ensure that

-- that, as that moves forward, safety of the patients is the number-one criteria that we're -- or criterion that we're looking at.

DR. GARBER: Okay. Yes, Dr. Satya-Murti?

DR. SATYA-MURTI: These are important comments. I want to ask, particularly Drs. Witten and also to you, have you been able to identify -- or Medtronic, for that matter -- retrospectively, some commonalities where patients have not done well?

I have some who have not done well. And it is my suspicion, in my own scanning of the literature, that those with preexisting dementia in whom testing has not been adequately done, particularly formal neuropsychological, tend to fare less well.

In any case, with the greater numbers that you have in your dossier, what, really, are some of the identifying features of those who have not done well, let's say, 3 to 12 months away from this?

And as far as publication bias, I agree with you Dr. Bakay, that I also have patients, and there are some in the literature, where tremors, especially MS tremors, where the surgery has been done, they have not done well. So we ought to give

cognizance to the fact those who have not done well have never entered the publication spectrum.

DR. MONTGOMERY: We have certainly had our fair share of patients who have not done as well as we would have hoped, and we have gone back and looked at the formal neuropsychological testing that we do always preoperative to try to identify some predictor of who is not going to do well. And our experience is -- like most other people's experience -- is that, while there are trends that one can identify as predictors, nothing with sufficient ROC -- area under the ROC curve reliability for that.

And, just anecdotally, the ones that we find -- in thinking back at the ones who did not do well -- one of the big issues is impulsivity, lack of self restraint, lack of self awareness, in terms of their limitations. And I think it's quite interesting. What we find is that often those sorts of things are very difficult to identify on specific neuro psych measures, and often families are unaware of it. And what we typically find is that their motor symptoms improve, but now they're in a position to be mobile enough to get into trouble, and then the families and the patients -- and the families get very concerned about that.

But, again, we take a very strict -- and perhaps one reason why we're not able to identify very specific predictors of outcome in that regard is that we have a very strict entry criteria. And so there's just not a lot of variance in our outcome that we can then parse back over the predictors to identify statistically what would be a predictor.

So, at this point, it's still very much a judgment on the part of the movement-disorders expert. I mean, I can't think of a single patient who's not -- who's had a completely normal neuro psych battery, and so it becomes a matter of exercising judgment as to what degree there is cognitive impairment and how it might relate on their ability to take full advantage of the improvement of their motor symptoms.

DR. SATYA-MURTI: That's why I'm asking about pool data. Has anybody looked at it in a case controlled study fashion backwards to see what could have been the features, those who didn't do well -- not just neuro psychologically, those whose improvement in UPDRS scores were just not as good?

DR. MONTGOMERY: Well, I can't -- I know that those are -- those are -- those kinds of studies and those kinds of analyses are underway,

and I can't speak to them specifically for deep-brain stimulation.

I can tell you of our experience with pallidotomy. And this is primarily in Dr. Lang and Dr. Lozano's group. And, again, we find things that are -- trend towards prediction, but nothing that -- nothing that I would feel comfortable as using as a litmus test to offer surgery to a patient or not. I think it requires considered judgment on the part of experienced physicians and surgeons.

DR. SATYA-MURTI: Wouldn't that be reason enough to be cautious in preselection? That's what we're talking about here.

DR. MONTGOMERY: But my experience working with physicians is that they do exercise that degree of caution, that they do exercise that degree of concern.

We have -- I can tell you in my own experiences that we have lots and lots of neurosurgeons that come and visit our institution, lots and lots neurologists who come and visit our institution with the idea of doing this surgery, and I can tell you that at least half of them that I've followed up have elected not do to the surgery, have elected not to do this, because they realize that

the investment that would be required to do it right is beyond what they're willing to invest. So at least my experience has been fairly positive in that regard.

DR. BAKAY: Yeah, I would -- I would also emphasize that, because, in teaching a number of these courses, one of the things that we're quite happy with is if they come and realize that they cannot do this -- you know, not just that they can do it, but that they can't do it. And there are certain situations when that may be the case.

I think there's a number of reasons for failure. One is selecting the wrong patient. Obviously, someone who doesn't respond, that certainly can be the case. We're not going to make dementia better, so patients that are demented, we try to avoid. There is the potential for cognitive impairment from the surgery, so obviously you run the risk of making those patients worse, so you -- but where exactly you draw the line is a difficult thing. You look at their MRI scans. If their MRI scans have all kinds of other disease, you try to avoid those patients also.

So there are criteria, but each of those criteria are relatively soft. And when the

pallidotomy experience, which is much broader -- I've done over 350 pallidotomies, but only about 200 deep-brain stimulators, so my experience there is much broader. But, even there, there is a difference of opinion as to what should be included and what shouldn't be included, in terms of the patient evaluation.

Then there are complications. And those patients you have to eliminate also from your evaluation, as the complication may have affected the bad result. And then, finally, you may not have been on target. And if you're not on target, then you obviously have the opportunity to correct that in this type of therapy, whereas you wouldn't with lesion therapy.

So there are a lot of reasons why you have failure, and there aren't good, hard criteria to say that there's one thing, or even a combination of things, that you should use for exclusion criteria. And, again, this is -- this is -- this isn't -- this is the area of the art of the surgery, in that one has to have experience. And one -- with experience, one gains the idea of what you can and cannot do. I think there's no way around that, that obviously the best surgery is -- are done by those that really

understand what it is that they want to do, have a great deal of experience, have good training. But that's, you know -- that's not something that you can somehow quantify, put a P-value to or --

DR. GARBER: Excuse me. Dr. Vatz and Dr. Witten, did you want to address the question? You've looked a great deal of evidence about -- are there anything that clearly -- any data that clearly indicate who -- people who do not seem to benefit, either because of high side-effect rates or because they simply don't get any efficacy from the procedure?

DR. WITTEN: Unfortunately, I can't really add anything to this. We don't have that kind of information based on the study. And that's why, as I say, the -- we had listed a number of populations as precautions, but we don't have any information that any specific population does not do well.

DR. VATZ: Just off the top of my head, from what I remember of the -- all of the small single-center studies -- I can't remember the details, but one of the studies in which half of the patients had a lot of MRI abnormalities -- it was an Italian study -- the patients with the MRI abnormalities tended not to do as well. Now, how

closely those MRIs were read -- you know, if they were huge MRI abnormalities or little bits of atrophy, you know, I can't tell, but that -- that's one thing that comes to mind.

DR. BAKAY: Yeah, that's the problem. Most of these patients will have some type of abnormality on an MRI, something of -- small or something that's major. And you have to sort it out as to whether this is something major and a patient to avoid, or whether this a minor problem that you can go ahead and proceed with the surgery.

DR. SATYA-MURTI: Dr. Garber, I'm not, again, saying the fact that there is no improvement. Obviously, I'm covering it, and I've been covering this for a long time. All I'm saying, in as much as there as there is publication bias, there is presentation bias, too. We are only hearing from those who have done well. Not to take away the credit for that, but we are not hearing from those who have not done well or what the reason is why they didn't well either. So --

DR. GARBER: Okay, thank you. You know, I'd really like to get to the questions. And we spent much more time on -- now, this discussion is very pertinent, but I would like us to frame it in

the context of the questions.

I'll recognize two other people who have had their hands up, and then that's it. We'll go to the questions.

Okay, Jim Rathmell, then Bruce Sigsbee. Or was it -- Kim, were you next?

DR. RATHMELL: I want to go --

DR. GARBER: Sorry.

DR. RATHMELL: I want to go to the question, so --

DR. SIGSBEE: Well, actually, this is directly relevant to one of the questions that we have. There is an age-related difference in the response. And the older age strata don't do quite as well. And I wonder if you could comment on that. Is that -- the biology of Parkinson's a little bit different in older individuals? Are the targets harder to find? Is it concurrent brain diseases? Or is it all of the above?

DR. BAKAY: All of the above. They do -- do not do as well as younger patients who have less disease or younger patients with more disease. That's just a part of the biology. You can't turn the clock back on those patients. You can't say, well, you know, you reach 66 and we're not going to

do these -- the surgery on you anymore.

It still is effective in those patients. If you look at those graphs, you'll still see that there are a number of those patients that do have dramatic improvements. There are just not as many of them in the most dramatic aspect as there are of the younger patients. They still do respond, and respond well, and I think that's the critical aspect.

This population that's going to be covered by Medicare will be a group that, for the most part, will respond and will respond reasonably well. It's not going to be as good as younger patients, but we can't bring them back to that younger age to do them earlier.

DR. MONTGOMERY: Yeah, I would agree. I mean, I think it's almost a matter of common sense. We don't expect our older patients are going to do as well as our younger patients.

I mean, we had a 47 year old who's running triathlons, and we certainly don't tell our older patients that they're going to experience anything nearly that dramatic. And older patients are more prone to complications and side effects.

But I can tell you we've operated on very

old 80 year olds who have done as well or better than some of our 50 year olds. Certainly one can draw a trend, but it is only a trend, and when it comes, then, to trying to predict what an individual older patient -- how an individual older patient is going to response, I think that's -- it's highly, highly problematic.

Again, going back to our detailed analysis of our pallidotomy data, we did see a trend, but the adjusted R-square for that -- it was very, very poor. Again, I think it requires judgment on the part of the physician. Is this a younger 75 year old, or is this an older 50 year old? These are the judgments that we're called upon to make in terms of individualizing any therapy.

DR. GARBER: Yes, Kim?

DR. BURCHIEL: One -- just one comment that might sort of tie this together. I mean, I think this has been a field that's evolved over the last five to ten years, and what's happened is things have settled out. I mean, consensus keeps coming up. And, unfortunately, that's the level of evidence right now for things like relationship to, you know, complications and certain demographic criteria of the patients, or experience, or any of

the other things we could enumerate today. We don't know, and we're just at the point now where we can begin to ask those relevant questions. That's why the VA study is going to be so important, the VA-NIH study.

So we're at that level of sort of class-three, maybe class-two evidence, right now on all those issues. You know, when you -- and when you look at the field -- what's happened over the last five years, what's progressed in the direction that we've avoided those things -- Parkinson's, plus; dementia -- you know, the age issue is sort of a plus-minus question at this point, is what relevance does that have to patient selection.

And I think there's some other criteria. Posture instability, we know, is not so well treated, but that's a kind of a subtlety. I think those are things now that we begin to ask intelligent questions, but we don't have the data to go to to answer specifics about level of training, relationship to complications and most of the other things that have come up today. We have a feeling of the answer, but we don't know the answers.

DR. GARBER: Okay, we're now going to turn to the voting questions. And I'd just like to point

out, the discussion questions are sort of questions that will help in the interpretation of how we answer the primary questions. And a number of these issues have already come up in the discussion, such as who is qualified to actually perform the procedure. So that's something that we will now revisit.

The first voting question -- Perry has put up the panel voting questions here -- is, "Is the evidence adequate to determine the clinical effectiveness for a well-defined set of Medicare patients with Parkinson's disease?"

And then if we conclude that, indeed, the evidence is adequate, we need to address the size of the overall health effect -- and, for the panelists, that is on the second page of the handout that -- the category's effectiveness are on the second page of the handout that has the voting questions.

So, first, I would like the panelists to consider this first voting question, which is really quite fundamental, "Is the evidence adequate to determine the clinical effectiveness?" We don't now have to say who that well-defined set of Medicare patients is, if we think that there is some well-defined set for which the answer to this question is

affirmative.

Irene?

DR. LITVAN: Yeah, I do believe that there is enough evidence that this is a breakthrough technology that has definitely changed the management of patients with Parkinson's disease and that the size of the response on those which the surgery is indicated is significant -- is approximately 50 percent, and I think that there is a lot of data coming from different centers -- multicenter studies, that would support that.

DR. GARBER: Yes, Dr. Weiner?

DR. WEINER: Yeah, I would -- I would reiterate what Dr. Litvan said. I think the evidence is adequate to support coverage of this. And, in particular, I'd point out that the -- I think, the last two drugs that were approved for Parkinson's disease by the FDA were the Ketochol and methyl transinhibitors, Entacapone and Tolcapone. And, in those studies, the pivotal studies increase the "on" time by about two hours. And the data here are suggesting that the "on" time can be increased by six hours.

So I can tell you, from using the drugs, that an increase of two hours of "on" time for

patients makes a tremendous difference to people. And sometimes even that little can be the difference between someone who has to live in an assisted-living facility or a nursing home, so that the possibility of increasing "on" time by six hours really, I think, does qualify as a breakthrough therapy.

DR. GARBER: Yes --

DR. SATYA-MURTI: I would say it's more effective, obviously, but I'm not sure it's breakthrough technology. I would say it's more --

DR. GARBER: Wait, wait. Let's defer the question until after we vote on this one. But, yeah, we will get to that if we answer affirmative to this one.

Yeah, Ken?

DR. FOLLETT: I have two comments, one of which actually relates to this last point. First of all, there has not yet been a study comparing deep-brain stimulation to best medical -- what we call best-medical therapy. But, as Dr. Montgomery pointed out earlier, we reserve this treatment for those patients who've really reached their limit with what can be done with medications.

The VA-NIH study was put together with

this consensus of opinion that deep-brain stimulation really is effective, and we wanted to look at some of the intricacies of its application. And I think the data support the fact that this -- the therapy is effective for those patients who have failed so-called best-medical therapy.

And I would also like to point out that, in the course of planning for the VA study, we did a survey of the centers of excellence that were recruited into the study to find out what their strategies have been over the last several years for the use of surgery for the treatment of Parkinson's disease. Notably, four to five years ago, most centers were still performing pallidotomies. And about two years ago, there was a very dramatic shift to where virtually every center, if not every center, virtually abandoned lesioning techniques and moved toward deep-brain stimulation. And in that sense, this really does border on what would be classified on breakthrough technology to where it has now become the surgical standard of care for the treatment of Parkinson's disease.

DR. GARBER: Any other comments? Tom?

DR. HOLOHAN: I don't know if any of the CMS representatives can answer this question, but

we've kind of floated a little bit around the idea of age. Mrs. Jante testified that her husband, who's in his 50s is a Medicare beneficiary. Does Medicare have any data on the average age of Parkinson's disease patients for which Medicare is responsible for coverage?

MR. BRIDGER: We have a number of beneficiaries under 65 who fall into the disability category, but I don't think we have the age number. I think it's 12,000 --

MALE VOICE: Fifteen thousand.

MALE VOICE: -- 15,000.

MR. BRIDGER: Yeah, we -- I don't have any -- I don't have any specific numbers about the average age of the Medicare patient who has been diagnosed with Parkinson's, but there is approximately between 15,000 and 20,000 Medicare patients who are under the age of 65 who are disabled who have a principal diagnosis of Parkinson's.

DR. HOLOHAN: Okay, so -- so if we're, then, looking at a well-defined set, it sounds as though age is not an issue then, or may not be an issue.

DR. GARBER: Yeah, I -- this was something

that did come up on the conference call. I don't think you were able to participate -- were you -- I don't recall that you were on then. But that's right, the well-defined set does not have too many people over age 65. And I think most of us would agree with -- whatever that number is -- say, around 15,000 people -- that is a substantial number of Medicare beneficiaries who are at least potential candidates for this therapy and, I think the implication is, who fit within the range of patients studied in the literature.

DR. ZENDLE: Well, I just want to clarify, though. That does not limit it to only those Parkinson patients under age 65.

DR. GARBER: No, no, not at all. The question is, can you identify some set. It's just saying that that's a necessary condition, that's all, that there is some set.

Okay, so I would entertain a motion, if there's no further discussion, for -- regarding Question 1 about adequacy of evidence.

And let me just underscore, we haven't really, in the discussion, thus far, distinguished between subthalamic nucleus and globus pallidus, but the voting question should be about subthalamic

nucleus, unless the panelists would like to change the questions.

DR. SIGSBEE: Alan?

DR. GARBER: Yeah? I'm sorry.

DR. SIGSBEE: Could I suggest, based on earlier testimony, that there does not seem to be any clear evidence discrimination between the two targets, that we combine them in a single question?

DR. ZENDLE: I would second that.

DR. GARBER: Okay. Any discussion?

Could I just ask you for clarification? How, specifically, would you change the language? Is that "clinical effectiveness of STN or GPi" -- or it "and" -- what language are you --

MALE VOICE: Is there any benefit to -- (inaudible) --

MALE VOICE: Or.

DR. GARBER: Okay. Yeah, Steve, why don't you go ahead and --

DR. PHURROUGH: Even though we could combine them, I guess my question would be, is there a benefit to combining them, since we're going to answer the same question?

DR. SATYA-MURTI: Yes, there is, I would say, because there are other putative targets. If

we don't specify them by actual anatomic site, there is a tendency to -- for this to dilute into cerebellum and other areas. So I think it would be a good, from both science and coverage point of view.

DR. ZENDLE: And I think the idea of separating them was because there was some thought that there might be a difference in our conclusions. And I think that we all feel that there won't be, and, therefore, let's just do it together.

DR. GARBER: Okay. Bruce, did you have specific language that you want to use?

DR. SIGSBEE: That I was going to take the language here and just do "STN or GPi."

MALE VOICE: No, "and." There is evidence to determine the clinical effectiveness of both.

MALE VOICE: Yeah, yeah. Well, okay --

DR. SATYA-MURTI: If you say "and," it could call for targeting both sides, or one after the other serially, so I think "or" is better.

MALE VOICE: Well --

DR. SATYA-MURTI: And that leaves that option open. If you try STN --

DR. GARBER: I think there would have to be -- I think, logically, what Les says is correct,

it needs to be "and," because we're saying, I think, that both sites are effective.

MR. BRIDGER: Dr. Garber?

DR. GARBER: Yeah?

MR. BRIDGER: May I make a comment? I think one of the reasons why -- the reason why we separated the question so that Question Number 1 relates to the subthalamic nucleus, and Question Number 2, the same wording, asks the same question about the GPi, is because of the way that the assessment was performed and how we were looking at the evidence, breaking down the studies looking at the separate targets, so that you've got, broken down, by studies and numbers, results for the two targets.

So the benefit of combining the two questions potentially could confuse the issue rather than trying to keep them separate. And if your -- if your end result is the same for both questions, then that's the way it will go. But I think, for reasons of making it simpler to understand the flow of the review of the literature, they were broken down this way.

DR. SIGSBEE: Mr. Chairman, in the interest of time, can I withdraw my suggestion so we

don't have to --

DR. GARBER: And will the --

DR. SIGSBEE: -- discuss this any further and just --

DR. GARBER: -- seconder withdraw their seconding?

DR. ZENDLE: Yeah, but, you know, the reason we're having this difficulty is that some people are referring to, "Is there enough clinical evidence to make a determination," versus, "What should the coverage language say?"

DR. GARBER: Yeah, but --

DR. ZENDLE: And I agree that with the coverage language, you're going to have different language than when you talk about the evidence, so --

DR. GARBER: Well, I think what the --

DR. ZENDLE: -- I guess I was trying to be a purist about the medical evidence.

DR. GARBER: Yeah. I think in terms of what's going to work best in terms of advising CMS, CMS can be our guide there, so -- now, let me just say -- so that motion is withdrawn, so we're back to the original language.

But before we vote on this, we did have a

-- Michelle has pointed out that we had a session for open public comments in the afternoon, which we -- we should probably give public speakers who hadn't been previously scheduled a chance to speak now if they wish to address the issues. So let me just ask, is there anyone who would like to speak?

VOICE: (Inaudible.)

DR. GARBER: No, actually, in general, are you -- yeah, now would be the time to speak, even if it's not on this issue.

So we have one speaker. Is there anybody else who wishes to speak? Go ahead, Dr. Cohen.

DR. COHEN: Well -- hello? -- yes. I was a patient representative on the FDA panel that addressed this issue. That's now more than two years ago. So, as a patient and representing other patients, and particularly the patient who came here from Wisconsin to speak to you, I think that the time has come for Medicare to make a decision.

I'm -- I think the process has been dragging out a little bit too long. You've already heard from the panel that this is a -- deep-brain stimulation is the accepted medical practice in most medical centers, and pallidotomies are not -- no longer done. That's an important change that has

already occurred.

And, on the issue of quality, which, apparently, the FDA is -- outside of the quality of treatment and quality of care, which is outside the purview of the FDA, Medicare has a -- has a -- through the payment mechanism, has something to say about that.

One of the major issues of concern that came to me out of the FDA review of the -- of deep-brain stimulation was what has been discussed here earlier quite a lot this morning, the issue of the quality of the team, the quality of the surgeon, the quality of the neurologist. And in -- so that while you're doing the studies to refine the technique, I think there's a lot of patients that are waiting to be, sort of, liberated from their condition.

So the last point I wanted to make was that, with regard to quality, that Medicare can set the standards that the private sector will tend to follow, and that would be of benefit to the patient undergoing the surgery.

And that's about all. Thank you.

MS. ATKINSON: Dr. Cohen, before you leave, for the record, could you please state whether you have any financial interests or anything

to disclose.

DR. COHEN: No, I have no financial interest in -- and I came here under -- on my own nickel.

MS. ATKINSON: Okay, thank you.

DR. GARBER: Okay. Yeah, Steve has just pointed out that, procedurally, only the voting members of the panel can make a motion and second it or vote on it. And I would entertain a motion, with respect to Voting Question 1. Okay, yeah, you've got -- you want to read that?

MS. ATKINSON: For today's panel meeting, voting members present are Dr. Angus McBryde, Dr. Les Zendle, Dr. James Rathmell, Dr. Bruce Sigsbee, Dr. Kim Burchiel, and Dr. Thomas Holohan. And the chairperson, Dr. Alan Garber, will vote in the event of a tie. A quorum is present. No one has been recused because of conflicts of interest.

DR. GARBER: Yeah, okay, so --

MALE VOICE: (Inaudible) -- the first question?

DR. GARBER: Now, I'd like to call for a motion. The first question is the one that is on the screen there. We -- the motion to amend that question has been withdrawn, so -- but we don't have

a motion on the floor.

DR. ZENDLE: So moved.

DR. SIGSBEE: Second.

DR. GARBER: Okay, which is approval of -- and answer --

DR. ZENDLE: Question 1.

DR. GARBER: --affirmative? Is that what the motion is? And there was a second.

Any further discussion? We're right now only considering, "Is the evidence adequate?" Okay, voting members only.

MS. GREENBERGER: Excuse me.

DR. GARBER: Sorry.

MS. GREENBERGER: May I just make a comment? I'm not a voting member, but I didn't make a comment during the discussion. My comments really will pertain to the effectiveness criteria, because I sense that there's a consensus that the evidence is adequate, but I wouldn't want to go without saying that I believe it certainly is.

DR. GARBER: Okay, thank you.

Okay, so all in favor of the motion, which is to answer the first question in the affirmative?

(A unanimous show of hands by the voting members.)

DR. GARBER: Opposed?

(No response.)

DR. GARBER: Okay. Now, just for reporting purposes, because I will need to present our deliberations to the executive committee, if any individual member could just give me a statement about why they believe the evidence is adequate. This is -- I'm not questioning your vote, but I will need to report what the critical items of evidence were. So does anyone voting in the affirmative care to answer that? Kim?

DR. BURCHIEL: I would submit that the evidence, although not class-one evidence, is so consistent in the variety of studies and the outcomes that the evidence is -- I think, somebody whose word "compelling." I think Joan used that. I think we have detailed reports now from FDA, from BlueCross TEC assessment, and representatives from industry and from academic, neurology, neurosurgery -- they all attest to the compelling evidence. And I was swayed by that.

DR. GARBER: Okay. Bruce?

DR. SIGSBEE: I'd like to perhaps amplify on that. One of the concerns has been it's been compared in a randomized way to best medical

treatment. In a certain sense, it is, in that the patients serve as their own controls. Presumably, they've already exhausted medical/pharmacological intervention. And then there's a 12-month comparison to their pre- and postoperative state. And perhaps that's one of the cleanest controls you can have in this circumstance. So I think that there is very solid science behind this procedure.

DR. GARBER: Anyone else? Okay. Oh, yes, sorry. Go ahead, Angus.

DR. MC BRYDE: I believe they ought to be included, since this is a substitute. This is actually a next generation that's more effective than the procedure, ablation and so forth, that we had earlier. So that should be looked at as a continuity to -- (inaudible).

DR. GARBER: Okay.

DR. HOLOHAN: I also think that the evidence indicates that the risk-benefit ratio is reasonable in these patients.

DR. GARBER: Now, a -- I'd like to just ask the panel's sense. Rather than answering size of effect now, would you care to vote on the second question about GPi before we address size of effect, since the panel seems to think that they were --

there's little reason to distinguish the two sites? Would that be the way people would like to proceed?

Okay, so then I'll entertain a question about that first bullet under Panel Voting Question 2, which is identical, except it says "for bilateral internal globus pallidus" instead of "subthalamic nucleus."

DR. RATHMELL: So moved.

DR. ZENDLE: Second.

DR. GARBER: A yes vote will be an answer in the affirmative on this one. Any discussion? All in favor?

(A unanimous show of hands by the voting members.)

DR. GARBER: Opposed?

(No response.)

DR. GARBER: And may I infer that your reasons for voting in this way on this question are the same as on the last one?

(Panel indicating in the affirmative.)

DR. GARBER: Okay. Thanks. For the record? Okay.

MS. ATKINSON: For the record, the first question, "Is the evidence adequate to determine the clinical effectiveness of bilateral subthalamic

nucleus deep-brain stimulation for a well-defined set of Medicare patients with Parkinson's disease," the vote was unanimous.

The second question, "Is the evidence adequate to determine the clinical effectiveness of bilateral internal globus pallidus deep-brain stimulation for a well-defined set of Medicare patients with Parkinson's disease," the vote was unanimous.

DR. GARBER: Okay, thank you.

Now, we will address that second bullet, which is -- oh, yeah, I think that would be helpful, Perry, if you put on the category's effectiveness. That is how effective is, "We have determined that there is adequate evidence to conclude that it's effective." And now we need to assign it to a category.

DR. ZENDLE: Point of information?

DR. GARBER: And again, we can choose to have the discussion in terms of both GPi and STN combined or separately.

DR. ZENDLE: Point of information?

DR. GARBER: Yes, Les?

DR. ZENDLE: I want to try to understand a little bit -- and maybe, Alan, you're the person to

answer this question -- the difference between "breakthrough technology" and "more effective." I was struck that "more effective" uses the words "small benefit," and the "breakthrough" implies a "large benefit," but then also uses the words "standard of care."

And I think we've talked about that this probably is the surgical standard of care, but does not replace medical therapy. It's only after medical therapy has failed. I'm a little worried that if we just say it's -- "breakthrough technology" is now the standard of care, that it might imply different than what I just said.

And I wonder, is there a way to clarify that, or are we really stuck with these -- just those two choices?

DR. LITVAN: Well --

DR. GARBER: Well, just -- sorry?

DR. LITVAN: No, I was going to say that it becomes the standard care once the medical treatment has failed, and I think that -- that is what is missing.

DR. GARBER: Yeah, and, as a procedural point, if we want to use the language that Dr. Litvan just suggested, that's something the panel is

free to do to clarify it.

Tom Holohan was also a part of those discussions. And this is the language that the executive committee chose to adopt. We have not had a lot of experience. We've had some experience assigning interventions to these categories of effectiveness, and I think we should view these as guidelines. But if there's a problem with the language, the panel should feel -- I think we should try to fit within these categories, but if we have a good reason to say we want to modify them in some way, then that -- the panel should feel free to do so.

Tom, did you want to comment on the categories at all?

DR. HOLOHAN: And maybe frame a motion that says it the way we would probably vote affirmative on it.

DR. GARBER: Thank you very much.

(Laughter.)

DR. HOLOHAN: I think that the sticking point with "more effective" is the issue of a "small effect" or the perception of a "small effect." I think that all of the data on both of these procedures provides at least evidence of a "moderate

effect," not a "small effect."

I'm concerned about the use of the word "breakthrough technology" for the reasons that I think you've eloquently expressed.

Would the panel agree to use the phrase "more effective" with a modifier, which is "more effective showing -- with evidence showing a moderate improvement in patients who have failed medical therapy" -- in lieu of "breakthrough technology"?

DR. LITVAN: Can I --

DR. ZENDLE: That doesn't address the pallidotomy-versus-stimulation issue, which I think -- I am impressed that it basically has become the surgical standard of care in people that have failed -- although once improved, but now failed medical therapy.

DR. LITVAN: So it is standard of care, and so it should be "breakthrough."

DR. ZENDLE: For people who qualify for surgical therapy, it is --

DR. LITVAN: It is the --

DR. ZENDLE: -- the standard of care.

DR. LITVAN: -- standard of care, and so it is a breakthrough.

DR. GARBER: Yeah, I think that if you look back to the page with the discussion questions -- the discussion questions, two of them are getting at the idea, really, of who is the right candidate population. And it is perfectly appropriate for this panel, in assigning this to a category of effectiveness to specify in which patient population that that classification -- so, for example, you could conclude that it's marginally effective, or even harmful, in some subset of patients, yet a breakthrough in another.

And I believe that what we should do insofar as this information is address this for the -- for all the relevant patient populations that have been studied.

Now, Dr. Litvan, Dr. Satya-Murti, and then Dr. Sigsbee.

DR. SATYA-MURTI: On -- I would be more comfortable if it said "moderate" instead of "small," because, as we have seen, it seems to be more than small. The reason we've been avoiding standard of care is that, were it to be standard of care, then the question will come -- on this instances where this was not performed, then the question would come, Did you not know that this is

the standard of care? Why was this not given the treatment of choice? And these may be frail patients and so on, so it may have a legal tentacle that extends by calling it "standard of care," meaning that that's what they should have.

So the improvement is moderate. Until we get further data as to which candidates are ideal, I would prefer that it not be called "standard of care" yet, because that seems to be the only way to qualify it to "breakthrough technology."

DR. HOLOHAN: What you're saying is if you don't get it, you're getting substandard care.

DR. SATYA-MURTI: If you're not given the surgical option, that's right. The implication is putting as "standard of care" -- because it's language -- the phrase "standard of care" finds application in CFR and Medicare regulations in multiple places. So, you're right, the negative implication of that is, why did this patient not get the standard of care? So at least avoid that. The "moderate" would avoid putting in -- boxing it into either --

DR. HOLOHAN: I would support striking the "standard of care" terminology for every reason that he said, plus many others. Setting a national

standard of care would have implications even beyond Medicare, and I think it would be -- it's awkward and unnecessary.

I think all you're trying to do is differentiate, I think, for all panelists, is the difference between the "small effect," which is more effective than a -- you can call it "moderate" or "large" or whatever. But I would support striking language that refers to "standard of care."

DR. PHURROUGH: Let me make just a procedural comment here. These categories of effectiveness were defined by the executive committee and given to the panelists to use. So I believe what we need to do is, if you have some disagreement with the categories, is not change the categories, but to modify it. So what's asked for in the guidelines --

DR. HOLOHAN: What's the difference between "change" and "modify"?

DR. PHURROUGH: You -- what the recommendation should be is that it falls into the category or "more effective," but -- or falls into the category of "breakthrough technology," but not say we're going to change the definition of "breakthrough technology," since those definitions

have been given to us to use.

DR. ZENDLE: Could a member of the executive committee give us an example of what they consider -- or what has been classified as a "breakthrough technology"?

DR. GARBER: There hasn't been one yet that the executive committee has reviewed. But, also, I appreciate what Steve said, except, as one of the authors of these, I thought that these were going to be subject to revision, and I think that the panel can actually help the executive committee by identifying areas where these definitions of the categories don't seem to work.

And what -- if I captured the sense of the panel correctly, I think the panelists who have spoken are uncomfortable with saying it's standard of care, but it's also not simply a small improvement. It's something that's a substantial improvement. And what I hear you saying is that it's substantially more effective, which is somewhere between what the executive committee called "breakthrough" and what it called "more effective."

And I believe, Steve, if I'm correct, that it would help the executive committee to have the

panel make a determination, like "it's substantially more effective" without necessarily buying into the exact language in these two categories.

DR. PHURROUGH: You can make whatever recommendations and -- to the change of these to the executive committee, but I don't think we need to change the definitions, as they are. We can recommend that the executive committee change them, but we can -- I think you can -- you can "qualify," if that's the better term, qualify what those definitions are.

DR. ZENDLE: I'll make a motion, if you'd like.

DR. GARBER: Okay. Well, Dr. Litvan had her hand up, so let --

DR. LITVAN: What I wanted to say is that one way to go around this is to say "for those patients in which this is indicated." So you're going to select a set of patients. And, obviously, this is not retrospective, but prospective, because this is new technology. It's not something that existed ten years ago.

So I think we should -- can be less concerned if you really think that these patients -- there is an indication for a patient. But I think

that if you don't say that it is a standard of care, someone may say that they -- the patient may not qualify with not real reasons for not qualifying it, and they will definitely get a substandard of care, because, at the present time, if the patient has certain features that is not responding to the medication and has the appropriate good health and the diagnosis is appropriate, it should undergo this kind of surgery.

DR. GARBER: Okay, well, then you can vote to say that it's "breakthrough," if I understand correctly.

DR. LITVAN: Well, I think that if you do make some qualifications to this --

DR. GARBER: About which -- the patient population applies to it.

Okay, Les was next and then Bruce.

DR. ZENDLE: Just to get something on the table. I would make a motion that we -- the panel approve a statement that says that "this technology" -- and it would be the first one, I guess -- "is substantially more effective than the ablative surgical option in patients -- in these selected patients," or however you want to word it.

If you just say "it's more effective than

other surgical options," then you get into the STN-versus-GPi thing, and I don't want to do that. So I think if we just say that it's "substantially more effective than the ablative surgical option," I think that would --

DR. WEINER: No, I don't think that's going to work, because I don't know that we have evidence about that, that DBS is substantially better than an ablative option. I don't think that's the question.

DR. GARBER: Well, the issue -- well, okay, we -- we will have to say what it's compared to. But, right now, we are -- the voting question was about the evidence, and I suppose we can -- we probably should have said what it was compared to when we were voting on whether the evidence was adequate, but it's -- it's compared to some alternatives that we thought that the literature addressed.

DR. LITVAN: (Inaudible) -- is medical care.

DR. GARBER: Yeah, so maybe it's against medication. But, Bruce, you had your hand up?

DR. SIGSBEE: I think we should strike discussion of "standard of care." Standard of care

often has nothing to do with efficacy, and I know there's a lot of things in medicine that are considered standard of care, but there's no evidence that they're effective and -- for example, Heparin with strokes.

The -- it's a semantic discussion here. And "more effective" implies that you have something to compare it to. And is ablative surgery truly comparative? In this circumstance, you have a bilateral technique that improves overall motor function, compared to a unilateral that, at best, improves just one side of the body. And if you don't have a good comparative intervention, then it -- presumably "breakthrough" is the word to use.

I am a little uncomfortable with "breakthrough," because it's somewhat of a dramatic term and it -- you know -- (inaudible) -- standard -- (inaudible) -- going out, we have breakthrough, this, that, or other thing. And perhaps a somewhat different term needs to be crafted to indicate that, at least at this point, there is no equivalent technology to provide this particular treatment for patients.

DR. BURCHEIL: Could I make a friendly amendment to the motion on the -- there is a motion

on the floor, isn't there?

DR. GARBER: No.

DR. ZENDLE: It has not been --

(inaudible) --

DR. GARBER: Well, it didn't get a second.

DR. ZENDLE: It sort of -- go ahead and -- what's your suggestion?

DR. GARBER: Unless there's a second, it will fail for the lack of a second. There's no second, so there's no motion on the floor.

DR. BURCHEIL: (Inaudible) -- amendment.

DR. ZENDLE: So make a motion.

DR. BURCHEIL: To bypass this and squeeze in another category here called "substantially more effective," with the language being, "The new intervention improves health outcomes by a substantial margin, as compared with established services or medical items."

DR. ZENDLE: Great.

DR. GARBER: I'm sorry, I couldn't hear the last part. As compared with what?

DR. BURCHEIL: Same language. I'm just putting in "substantially more effective."

DR. GARBER: Oh, okay. It says "compared with established services."

DR. BURCHEIL: "The new intervention improves health outcomes by a substantial margin, as compared with established services or medical items."

DR. SATYA-MURTI: Either that or more than -- (inaudible), because the binding and obligatory effect of standard of care is somewhat fearsome, I think.

DR. ZENDLE: I'll second his motion.

DR. GARBER: Okay, so we have a motion that's seconded. Tom?

DR. HOLOHAN: Let me make an observation. We've talked about effective compared to what, and people have proposed unilateral or destructive lesions. In fact, all of the data that appeared in the BlueCross TEC assessment was basically relevant to medical therapy, drug therapy. None of those studies were comparative. There never has been a comparative study done of destructive lesions -- GPi, STN. All of the data we have compares it to medical therapy, and I think we should restrict ourselves to that.

DR. GARBER: So there's a question -- Kim, your proposal was to apply the category of "substantially more effective," as you defined it --

DR. BURCHIEL: Yes.

DR. GARBER: -- to -- at this point, we're talking about STN. Then there's an option that we have, I believe -- and, Steve, maybe you can address this -- which is to explain what we mean it's compared to. And I don't think that has to go into the -- answer the question, but can be in the explanatory text. In which case, what Tom just said would appropriately appear as an explanatory point under this main motion. That's just a procedural question. And, Steve, does that --

DR. PHURROUGH: Yeah. I think, as Kim's motion, I think, takes into account my concerns of changing categories, versus adding or qualifying --

DR. GARBER: Uh-huh.

DR. PHURROUGH: -- and then leaving it, as Kim moved, and then explaining that would procedurally be appropriate.

DR. GARBER: Okay, so -- now -- so the other aspect to this is, we can vote on this question and then we can get the sense of the panel about whether they want to make the qualification that Tom suggested or any other qualifications, for that matter. Is that okay, procedurally?

So we just first vote on Kim's motion,

which is actually the motion that's on the floor.

DR. ZENDLE: Second.

DR. GARBER: Okay. Any further discussion? And maybe we could read that again. Kim, would you mind?

DR. BURCHIEL: Substantially more effective. "The new intervention improves health outcomes by a substantial margin, as compared with established services or medical items."

DR. GARBER: Okay. All in -- any further -- Joan?

MS. SAMUELSON: I do have a comment, yeah, which goes to the definition of "breakthrough," I think, and -- and the relevance of pallidotomy. I'm a lawyer by training, so the distinctions make a difference to me, although I apologize for not having the scientific background. But my lay understanding is this really has shelved some of the ablative surgery as the standard of care, because they were available because some alternative to the medication was so desperately needed because there was no alternative, and people were willing to take the risks associated with pallidotomy. And they're not being conducted now, because there is this alternative, so there is a relevance, I think.

DR. BURCHEIL: Can I answer that, as an active practitioner in this field? Is that the ablative options haven't disappeared.

MS. SAMUELSON: I understand they haven't disappeared. It's certainly -- from a lay patient perspective in the community --

DR. BURCHEIL: It -- they simply represent another alternative, and there has been a shift in the field -- a massive shift, albeit, but towards deep-brain stimulation, but pallidotomies are still being done --

MS. SAMUELSON: Right.

DR. BURCHEIL: -- thalamotomies are still being done. I mean, these are still being done. It's just another arrow in the quiver. So we have now an important technology which, in most aspects has supplanted ablative procedures, but it hasn't completely eliminated them.

MS. SAMUELSON: I -- and I understand that. I think the fact that it is a massive shift goes to the issue of how breakthrough it is, and I appreciate that that sounds a bit dramatic, but it -- I think it's a profound new option, and "breakthrough" is a word that makes sense to me.

DR. SIGSBEE: Our role is to comment on

the quality of the data. And, at present, we do not have good comparative data to ablative procedures. And so that, based on the science and the evidence here, I'm not sure that we can make that statement.

DR. GARBER: Yeah, I think that that's the crux of the matter here, which is that we had a very carefully done review that was addressing a somewhat different question than the one that you just raised. So, you know, we haven't had the same kind of systematic review of the evidence that it's superior to, say, thalamotomy. And consequently, it leaves us in an awkward position, because we're really talking about what we've looked at the evidence for, and the panelists could still conclude it's a breakthrough, in which case they need to vote against this motion. Or you could say that, based on literature, according to Tom's qualification there, that it is substantially more effective.

MS. SAMUELSON: My concern was that maybe the tail was beginning to wag the dog, that the concern about the comparison within -- between surgeries was encouraging a downgrading, a bit, of the overall significance of this, and that that's what the motion would be doing, when there's several other indicators that this is a profound new option

-- the possibility of reduction of medication, the increased "on" time -- the enormous increase of "on" time in some cases, when that is such a massively important factor in the life of a person who's living with Parkinson's, and the consequences of it for them.

DR. GARBER: Yeah, well, you know, I think that one thing that's important to keep in mind is we knew it would be hard to assign interventions to categories. We had a lot of discussions about wording in categories, and so on.

It's important to keep in mind that all of our discussion today is going to be part of the public record. And I can't speak for CMS, but I imagine this is not going to make a big difference, which category we assign it to, in terms of their coverage decision, because we've concluded already that there's adequate evidence. And if we also conclude that it's substantially more effective -- I think we've given very clear guidance to CMS that we think this is something that should be covered.

DR. ZENDLE: I have a question --

DR. LITVAN: Well, I agree with what you're saying, but I think her point is well taken. This has dramatically changed our practice in

neurology, and I think that needs to be reflected in some way.

DR. GARBER: Yeah, but the people should vote -- if you believe this does not belong in the category "substantially more effective," you should vote against the motion that's on the table and, instead, offer another motion for assigning it to a different category. But right now, we'll just vote on whether it's substantially more effective.

DR. SATYA-MURTI: The language we choose here, I don't think will change its availability. If we overstate the efficacy, there is a chance it will be inappropriately performed. So that I don't think whatever language we choose here will change the availability of this procedure to individuals who need it.

DR. GARBER: Ken?

DR. FOLLETT: Just one additional point. We don't know for a fact that deep-brain stimulation is more effective than pallidotomy, because the issue has never been studied. We believe that it's safer. For example, there are few, if any, neurosurgeons who would perform bilateral pallidotomies anymore, but it may be that bilateral pallidotomy is every bit as effective, clinically,

as DBS. We simply don't know. It's just that DBS appears to be safer.

Okay, thank you.

DR. LITVAN: Well, we do know that it has more side effects, though -- bilateral --

DR. FOLLETT: It is safer. That's what I meant to say.

DR. GARBER: Yeah. Yeah. Okay, all in favor of the motion, say aye.

(A chorus of ayes.)

DR. GARBER: Opposed?

(No response.)

DR. GARBER: Okay.

MS. ATKINSON: The motion that was on the table is that, "substantially more effective, the new intervention improves health outcomes by a substantial margin, as compared to established services or medical items," was unanimous.

DR. GARBER: Okay, and --

DR. ZENDLE: I would move the same language for the second question.

DR. GARBER: Okay, so for GPi, same question.

DR. HOLOHAN: Second.

DR. GARBER: Second. Okay, any

discussion? All in favor?

(A unanimous show of hands by the voting members.)

DR. GARBER: All opposed?

(No response.)

DR. GARBER: Okay, now, the next thing is just an issue of guidance, and I don't know that we need a formal vote, but I want to get the sense of the panel about whether they concur with the point that Tom Holohan made about the fact that the literature that we have reviewed really applies to the comparison with medical therapy.

DR. BURCHEIL: Can I -- can I address that for --

DR. GARBER: Uh-huh.

DR. BURCHEIL: It does, indirectly. Because by entrance criteria, the studies we have basically say these are patients that are previously levodopa-responsive that are now medically intractable. But, as Ken's pointed out and a number of other people, we don't have a study which compares to medical therapy, period. So it's a little weaker than a comparative analysis.

DR. FOLLETT: I -- yeah, I thought I said that.

DR. BURCHEIL: Okay, maybe you did.

DR. LITVAN: Well, you have -- yeah, it's true that there isn't, because there hasn't been any --

DR. BURCHEIL: It hasn't been done.

DR. LITVAN: -- yeah, a randomized study that would do it. But, on the other hand, there is no other possibility than -- (inaudible) -- history.

DR. GARBER: Tom, do you want to just restate what the point is?

DR. HOLOHAN: Yeah. If you look at the published studies that made up the bulk of the BlueCross/BlueShield Technology Assessment, the improvements were, for the most part, recorded in the UPDRS score. And those were improvements comparing patients' post-treatment with stimulation to pretreatment. And there were some that -- some comparisons of "on" and "off" with stimulation.

So the direct comparison was really in improvements in the UPDRS, for the most part, using deep-brain stimulation of either the STN or GPi, or not using it. So the direct comparison, although not prospectively randomized controlled trial, was with medical therapy available to the patients at the time.

There was no comparison between STN and GPi -- the VA will do that. There was no comparison bilateral versus unilateral. And there was no comparison of deep-brain stimulation versus ablative therapy.

So, although an imperfect comparison, it's the only thing we have, in terms of a measure of effectiveness of DBS of either the STN or GPi compared to anything. The comparison was toward the responses to medical treatment, drug therapy.

DR. GARBER: So -- well, this is going to anticipate the discussion about who this generalizes to. I know this is an oversimplification, but could we put it that it was comparing these therapies -- that is, DBS in the different sites, with little ability to distinguish between the effects of the sites -- to continued standard therapy among patients who had failed medications?

DR. HOLOHAN: Yes.

DR. GARBER: Would that be just a fair -- I realize that that's not a hundred percent true, but it might be -- is that a fair simple statement of what -- (inaudible) -- so I can --

DR. ZENDLE: Could you just add "who have previously responded, but now are" --

DR. GARBER: Yeah, "who had some evidence of response to -- "

DR. ZENDLE: -- "but who now are not responding."

DR. GARBER: -- "are not responding adequately." Would that be fair?

(Affirmative responses.)

Okay. So that will give, I think, CMS some guidance about who we think this applies to. And would it also be fair to say that we don't see strong evidence of differences by age sufficient to say that the results do not hold, say, for the elderly, as opposed to the younger people with Parkinson's"?

(Affirmative responses.)

DR. GARBER: Okay.

DR. HOLOHAN: Can I comment on that?

DR. GARBER: Sure.

DR. HOLOHAN: The data that Medtronic provided us -- and this one of the reasons I was trying to beat on CMS about age distribution to their patients -- there were a couple of categories where there were statistically significant different differences in adverse effects in age, broken down into over 65 and under 65 -- cardiovascular

disorders, confusion, and, probably more importantly, paresis, hemiplegia, and intracranial hemorrhage.

Now, it's true that most of the -- most, but not all, of the intracranial hemorrhage in the studies in the reported in the BlueCross/BlueShield TEC assessment were not major. A few were. But hemiplegia is a very significant adverse effect, and it occurred almost five times as frequently in people over the age of 65 as in people under the age of 65.

So I don't think we can be too cavalier about saying there is no relationship between adverse effects and age. I'm not sure how you can craft that.

DR. ZENDLE: Yeah, well, I -- while there is no -- while you can't say there is no relationship between adverse effects and age, I think the point is -- is that age alone is not the determining factor. And I can't remember who said -- but there are older patients who do very well and don't have complications, and there are younger patients that can have complications. It's a factor to consider by the clinician, but I don't think that, in terms of stating that there's evidence to

determine clinical effectiveness, should be affected by age.

DR. LITVAN: Probably it's related to associated disorders that occur in aging as you see that also vascular events, in general, are increasing in age population.

DR. HOLOHAN: All that's true, but that's not -- that's not the point I made. The point I made was that the proportion of adverse, some very serious, at least based on the Medtronic data, clearly relates to age. And I don't think we can make a differentiation in terms of which patients are suitable, but I think it would be perhaps a -- I don't want to use the term "irresponsible," but I think that it's appropriate that we make some comment about the apparent increase in age-related adverse effects.

DR. GARBER: Ken, did you want --

DR. SATYA-MURTI: One problem I had with that age was, that's the age at which surgery was done, but it doesn't reflect on how long they've had PD and how badly they've done with meds. So it may be not only age itself, but also the poor responsiveness over the years. This person operated at 66 may have had it from 25; whereas, the next 66

may have had the onset only at the age 61 -- clinical onset. So --

DR. GARBER: Well, just -- in the interest of moving this to a relative statement, maybe I can try paraphrasing Tom a little bit and see if I have the agreement of the panel, which is that there is evidence of continued benefit with advancing age, and also evidence that risks of the procedure increase with age.

Ken?

DR. FOLLETT: Yeah, I span these two points that we heard from Dr. Bakay and Dr. Holohan. With -- there are increasing risks of surgery for almost any surgical procedure with advancing age. It was Dr. Bakay's point. The older the patient, the more likely there will be some type of complication. But, on the other hand, I agree that perhaps we need some comment about the impact of age.

I'm very concerned about making a strong statement based upon the Medtronic data, because those came from an entirely unselected patient population. We don't know why patients were offered STN implants versus GPi implants. Perhaps the more infirm patients were the ones who tended to have the

GPi implants. And the site of implant in the Medtronic data was determined solely at the discretion of the implanting physician. So I think the --

DR. GARBER: Yeah, well, I have to say, by the way, that we almost always are in a situation where we don't have a lot of data on subgroups defined anyway, whether it's age or other clinical characteristics and so on. And so we would have to qualify anything we said by noting that we had either small numbers, which is the case here, or not such great -- not such well-designed studies.

DR. LITVAN: Has anyone analyzed the hypertension or history of coronary disease?

DR. HOLOHAN: No.

DR. LITVAN: No?

DR. HOLOHAN: No.

DR. GARBER: Bruce?

DR. SIGSBEE: I would be very hesitant, based on this Medtronic data, to make that statement. If you look at several of the categories, in fact, they're more frequent in the younger age group. And you have to remember, statistics is looking at what's the chance that this occurs on a random basis. You're looking at so many

criteria that some of them, just on a random basis, may be more in one group than another. And the numbers are very small here. So I think we have to be very careful about making assumptions based on the statistics presented here.

Now, I think we would all agree that probably this is more risk as one gets older, but I -- but the -- given the numbers, I'm hesitant to really support that statement.

DR. GARBER: So the -- but we're left with the question, if we are asked, "Is there any difference with age?" That is, are people who all -- they're as well off, not as well off, better off, compared to people who are younger -- getting this procedure. What should our answer be?

DR. ZENDLE: I think your statement was accurate, that they -- they benefit, but there tends to be higher complication rates in older people.

DR. GARBER: And that the evidence base -- I'd further qualify that by saying that the evidence base is very thin.

DR. BURCHEIL: Why don't you just say that the evidence is inadequate to answer that question -- I mean, that the absence of proof is not the same as proof of absence.

DR. GARBER: Well, this is an example where we will be asked about: Is there any indication of trends? And you can say either there are or there are not trends, and then you can -- you certainly have to -- have to say that the evidence is insufficient to draw any firm conclusions.

DR. LITVAN: I think there is evidence that -- enough evidence that there is some benefit, but there is not -- and perhaps more complications. And so you can say those, that -- but the numbers are not --

DR. GARBER: And the -- and the study designs are not such that you can draw --

DR. LITVAN: Right. I mean, the question has not been addressed in a specific study, so conclusions cannot be hard.

DR. SIGSBEE: Perhaps we can just simplify it by saying that, for the age group over 65, there is evidence that it is an effective intervention with a reasonable risk-benefit ratio.

DR. LITVAN: With a what?

DR. GARBER: But that's -- that's not what I think I've heard, which is -- you can't reconcile that with there not being a lot of evidence separately for the over 65.

DR. SIGSBEE: But, I think, rather than -- than looking at it compared to the under 65, you're looking at just the total complication rate for that age group for inter-operative and other complications, that it still seems to be a reasonable risk-benefit ratio in that age group.

Do we -- do we have evidence that it is any -- clearly different than operating under -- under 65 on that?

DR. GARBER: That's a question of burden of proof. But I guess that, Bruce, one of the things I would have to say is where -- what we've seen good evidence for is in a heterogeneous population of patients, which includes both young and old, in fairly well-designed, though not perfect, studies, but fairly well-designed -- there is clear evidence that benefits exceed risks. But we're on much shakier ground with much more limited data when we try to stratify by age. I mean, it's --

DR. HOLOHAN: And the average age of the studies cited in the BlueCross/BlueShield TEC report was 58.

DR. ZENDLE: Alan, isn't the point that the conclusions we've reached, there's no evidence

for us to differentiate the effect between the under 65 and over 65? And I really think that's -- we should just leave it there.

DR. GARBER: Yeah, well, I would just say there is very little evidence to enable us to draw conclusions. And then -- about over 65 versus the under 65 -- and then we can say what the direction of the evidence is and point out that it's not really adequate. Are people comfortable with that?

(Affirmative responses.)

DR. GARBER: Okay. All right.

Now, we have a -- our big-three question, which is now the same technology -- or not the same technology -- it's unilateral thalamic DBS for a central tremor and/or Parkinsonian tremor for a well-defined set of Medicare patients with Parkinson's disease. Does anybody want to make a motion with regard to this question?

DR. ZENDLE: Can you clarify? That obviously wasn't part of the BlueCross/BlueShield TEC assessment, correct? That wasn't addressed in the BlueCross TEC assessment. So where is it addressed?

DR. RATHMELL: Have we had any -- and we've had no testimony. Although there was an in-

house analysis distributed to us --

(Inaudible colloquy.)

DR. GARBER: Yeah. Perry?

MR. BRIDGER: I'll comment on that question. The representatives from Medtronic presented data to you, as well as Dr. Witten, related to the initial study about the unilateral indications.

In addition, because the TEC assessment did not address the unilateral, we did a separate analysis of the unilateral evidence by using standard search methodology and generated a study descriptions table, which you all received in your packet, that outlined the findings of all of those studies as well as with some commentary after that.

So, in terms of the kind of evidence that you've received for the unilateral indications, although you don't have a formal technology assessment, you received those descriptions table as well as all of the articles and then the Medtronic and FDA presentation of that original data.

DR. LITVAN: And the evidence seemed to be that there is a clear benefit, and there was a reduced -- a reduction from almost -- from four to almost one in tremors.

DR. BURCHEIL: Can I say that the area of confusion here is we don't have a nice, clear-cut TEC assessment to go to and say, "This is what" --

DR. LITVAN: Oh, all right, but --

DR. BURCHEIL: But I -- we've heard -- we've heard references to the FDA, to BlueCross's prior assessment and also to current practice. I think Roy touched on that a little bit.

It's -- this is a dramatic effect. It -- in every way, it's at least as good as what we see with this other. And a very separate group of patients. I mean, we're treating tremor with VIM stimulation. We're not treating the cardinal symptoms of Parkinson's disease --

DR. LITVAN: Right.

DR. BURCHEIL: -- other than tremor. And we're also treating this other population of patients, which are essential tremor patients, which is, by some estimates, five to ten times more common than Parkinson's, so a huge impact on the Medicare population. And these patients are in that -- clearly in that age range. And so it's a little --

Hope we don't miss the point here. This is a huge effect. It -- the benefit is absolutely clear cut. And I'm sorry we don't have that

assessment to go to, but I can attest, as a practitioner, again, this is not a subtlety. This is a --

And this has been well digested by the movement-disorder field now, so much so that it's -- I think we're almost going back to this now because it never was touched on before, and it's been sort of lumped in to this discussion.

DR. GARBER: Jim and then Les.

DR. RATHMELL: So this is what I -- during our teleconference, was one of my principal discomforts here is that we had no summary of it, although we could have gone through individual -- you know, each of the studies were elucidated in the table. You had to really go and look at each one of those and then come up with your own reasonable summary. And your testimony is the strongest thing that I've heard. I came away with, "I don't know, but maybe the evidence isn't there."

DR. LITVAN: No, the --

DR. RATHMELL: It certainly hasn't been summarized for us in any understandable way.

DR. BURCHEIL: I think it's a process issue more than anything else. I think we backed into this, because it never -- this panel didn't

exist when this technology was approved -- or it was just in its very earliest days when it was approved by FDA. And that's the way things used to be done. And because it's DBS, because it's deep-brain stimulation, because it's movement disorders, it's being annealed to his discussion, but it really is, to some extent, a separate issue and -- but one, again, that's been very clearly documented in the literature.

And I think, again, as a -- just as a testimonial, you might look at the data. It's better than the data that we have for STN and GPi. And there's a nice study, for example, in the New England Journal comparing it to ablative procedures, like thalamotomy. We have more data for DBS for tremor than we do for GPi/STN.

DR. ZENDLE: So you're familiar with the process. How would you go about, as a non-specialist who's coming -- you know, the data is put before you a few weeks before this, and we don't have the data, yet we have to vote on whether we have enough data to make this assessment. How would you go about -- you know, we're here where we are. How would you move from --

DR. RATHMELL: Trust me.

(Laughter.)

DR. ZENDLE: Can you clarify? Because it appears to me that this is being promoted as being effective for suppression of tremor associated with either essential tremor or Parkinson's disease. Is that --

DR. RATHMELL: Correct.

DR. ZENDLE: -- true?

DR. GARBER: And that corresponds to what's been studied in the literature.

I actually -- I've got to say, I think Jim's criticisms are really good points. And when I received this, I was part of the BlueCross/BlueShield Medical Advisory Panel -- I think you were, too, Les, at the time --

DR. ZENDLE: Oh, two years ago.

DR. GARBER: -- yeah, when -- when we went over unilateral -- and the evidence was pretty compelling that it was effective, and it was similar to the evidence that you see for bilateral. And, you know, I -- so I didn't bother looking over all the articles again, and I know we all had the opportunity to do it, if we really wanted to, but -- but, I mean, basically, I think it's -- procedurally, this was not ideal.

But in terms of the substance, the evidence base was very similar. I mean, you can poke at the studies -- and this one thing where having a report -- an evidence report like we had for the other indications would be helpful, because you don't really know, without going through the studies, what their selection criteria were -- in great detail, although that was in the table. But study design flaws and so on, it's hard to get a sense for that.

But I can tell you that my recollection, having gone through this earlier, is that the evidence is very similar. It was pretty much equally compelling. And the effects, I thought, were, in broad terms, similar. So I didn't see this as very different. But I have to admit, it was based on evidence that we weren't presented with. I did have an evidence report available. And perhaps it would be better if everyone had had that evidence report, or a newly prepared one.

DR. SATYA-MURTI: I also agree this is an older surgery, but I'd like to add this applies only to ventralis intermedius. So I think thalamus is too broad, and it received multiple inputs -- somatosensory and so forth. So this needs to be --

data is there -- data are there, but it's only for VIM.

I'd like to ask the other panel members if they agree, instead of just saying broadly thalamus, which is huge compared to subthalamic region we are talking about, and as multiple representations.

DR. BURCHEIL: As Roy said, that's the target. I don't think anybody would disagree with that.

DR. LITVAN: Yeah.

DR. SATYA-MURTI: So we should make this -- (inaudible) --

MALE VOICE: Should we change the language, then?

DR. SATYA-MURTI: Well, you should be more specific. I think VIM is the most specific language -- ventralis intermedius, or VIM, and that's the one we had data on. And it even precedes STN and GPi.

DR. GARBER: Well, this would be a good time for a motion to -- we don't have any motion on the floor right now, do we? No, we don't. So if you have a motion with specific language, that would -- this would be an appropriate time.

DR. BURCHEIL: There's another -- one other issue, before amendments --

DR. GARBER: Uh-huh.

DR. BURCHEIL: Just one other thing I'd like to bring up, which was -- and I don't want to open up a can of worms here, but the -- I noticed in an ANS/CNS statement, they caught something that I caught in the BlueCross assessment, which was, effectively, that bilateral stimulation of the thalamus for tremor is not done because of untoward effects on oral pharyngeal musculature, dysphasia, dysarthria.

I can tell you, that couldn't be more wrong. It's done all the time, and quite effectively, and there is literature on this.

So, again, this -- we're going to pin ourselves down to unilateral thalamic DBS, which is what the FDA approval is for. We're really not hitting what is the actual practice today, which is bilateral stem. And, frankly, most patients that get this technology -- and I'd ask Roy or anybody else here that does this to comment on that -- or Ken.

DR. FOLLETT: Yeah, I would second that very strongly. I think it does some of our patients a real disservice to restrict this by language to unilateral applications. There are many patients

who undergo bilateral implantation of thalamic stimulation leads for treatment of bilateral tremor, and they do very well.

DR. GARBER: But do we have evidence? Do we have a complete assembly of evidence on bilateral?

DR. LITVAN: The problem, I think, is because of the history of bilateral thalamic lesion that caused a lot of side effects that this is not placed there and there are no studies to support it.

DR. BURCHEIL: Well, no, that's true. Actually, there are studies that are -- do incorporate substantial numbers of bilateral stimulation, though, but we don't -- (inaudible) -- hasn't seen that, and there has not been a specific technology assessment on that question, because it's not -- it's not been officially approved by FDA.

DR. GARBER: You see, one of the things to keep in mind is that if we haven't seen the evidence, it would be hard to vote affirmatively for this with broader language. And if we voted for it -- that this statement is true for unilateral, it doesn't say that bilateral is not effective or that there's not evidence. It just says we didn't address that question.

Tom, you had your hand up?

DR. HOLOHAN: Yeah, I don't want to sound too legalistic, but if we include bilateral, what we're basically doing is informing Medicare of our endorsement of an unlabeled use of an approved device. Now, Medicare has held, for a long time, that device approval for labeled indications is a necessary, but not a sufficient, condition for coverage. And we'd be doing that in this circumstance where we do not have the body of evidence presented to all of the members of this panel, as we have for DBS, for STN, and GPi. And I think that could put CMS in a very, very, very awkward position.

In the past, they have covered an unlabeled use of an approved device only in the presence of substantial -- one might argue, overwhelming -- evidence that that was appropriate treatment. And we're kind of pushing the envelope there, where most of the people -- I don't disbelieve our experts, but most of the panel members have not seen that evidence for even unilateral.

DR. GARBER: Okay. Well, thank you. We still don't have a motion on the floor.

DR. SIGSBEE: I'd like to make a motion.

DR. GARBER: Okay, Bruce?

DR. SIGSBEE: I'd like to make a motion that the -- that it is substantially more effective, with the same language that we've used before, than alternatives.

DR. GARBER: Well, we first have to -- we haven't -- we first have to address evidence adequacy on this one. We haven't voted on that yet. And we don't even have a motion on it.

DR. SIGSBEE: Well, I would like to make a motion that the evidence is adequate to determine that it is an effective therapy for central tremor and/or Parkinsonian tremor.

And I'd like to point out the Medtronic data. If I remember, the number was roughly -- it was for Parkinsonian tremor, it was -- the score of approximately 3.8 out of four to one, which, if you know -- if tremors -- this is a dramatic difference for somebody who is dysfunctional, versus very functional. And while not quite the same shift for essential tremor, a very similar one for central tremor. And, again, that's probably where the major use is here. And, again, it's somebody who's failed medical therapy and is responding to this. And our

medical therapies for a central tremor are somewhat limited.

DR. GARBER: All right. There was an earlier discussion about whether we wanted language as broad as "unilateral thalamic."

DR. BURCHEIL: Yeah, a friendly amendment to change that language as to "unilateral" -

MALE VOICE: Subthalamic?

DR. BURCHEIL: -- no -- "thalamic, parenthesis, ventralis intermedius, or VIM, end parenthesis, DBS. So qualify thalamic as ventralis intermedius.

DR. GARBER: Would you accept that as a --

DR. SIGSBEE: I agree, absolutely, yes.

DR. GARBER: Okay. So I'll take that as a motion and a second.

MALE VOICE: Does the word "unilateral" or "bilateral" or neither appear in the motion?

DR. GARBER: This was unilateral.

MALE VOICE: The motion was --

DR. SIGSBEE: Unilateral.

DR. GARBER: Unilateral.

DR. SIGSBEE: That's all we have the evidence for.

MALE VOICE: Okay.

DR. GARBER: Okay. Discussion?

DR. ZENDLE: Point of information?

DR. GARBER: Yes?

DR. ZENDLE: What are the consequences of us saying that we haven't really been presented this evidence and basically making no -- seeing no opinion on this? In other words, is there enough information from the -- answering the two previous questions that allows CMS to make their coverage determination on unilateral DBS?

MR. BRIDGER: Dr. Garber, may I make a comment?

DR. GARBER: Yes.

MR. BRIDGER: I just wanted to point out some issues with the thalamic, or VIM, data. The Medtronic approval data was based entirely on unilateral procedures. The data that's presented in the study descriptions that we prepared for you was not -- we did not search for unilateral or bilateral. So you'll see that the majority of those studies have patients that underwent bilateral VIM. It's hard -- I didn't break -- we didn't break down specifically the numbers, unilateral versus bilateral, but I think it's probably 60-40, unilateral versus bilateral, maybe 70-30.

Maybe one suggestion that I could make would be that you could consider the question, as written, but then, either with a motion or discussion, potentially discuss the fact that the bilateral VIM data doesn't seem adequate to make a determination or is not adequate for us to comment on at this point.

DR. SATYA-MURTI: If I may, I'd like to point out what happens, in practice. Usually, the contralateral side to the dominant side is done as unilateral, and the patient responds so well he or she seeks the other side. So it's often done -- I don't know if it's often, but it's -- I know, for a fact, instances where it's done bilateral, but in a staged setting. So would that be unilateral or bilateral? Because it's unilateral at one time, and -- (inaudible) -- with the requirements, but then it is bilateral eventually.

DR. HOLOHAN: Sequential unilateral?

MR. BRIDGER: Yes, that's right.

DR. HOLOHAN: And that's very difficult to pick up in the literature, because in -- typically, it was not reported in the studies whether the procedures were done at the same time or whether they were sequential.

DR. SATYA-MURTI: Yeah, simultaneous or staged. So to avoid that, I put down that simultaneous is not as warranted or as desirable as staged bilateral.

DR. GARBER: Well, in terms of how we should proceed, right now we have a motion and a second on a modified version of this specific question on the unilateral. And the minutes will reflect this discussion that we didn't have evidence on sequential bilateral versus simultaneous bilateral, or bilateral in any form, specifically broken up on this question. People have already made those questions. So, Perry, does that meet the needs of CMS?

MR. BRIDGER: CMS has not limited in its coverage to only things that this panel discusses, or -- (inaudible). So the fact that we did not present you evidence on bilateral doesn't prevent you from giving us some suggestion that there might be evidence for bilateral. It's not something that you would vote on, since it's not a vote in question, but we certainly will take that information and could make a coverage decision that included bilateral thalamic if we did our own evidence search and found it.

DR. GARBER: Well, I guess -- at least I don't feel comfortable using our process to discuss a question where we haven't been presented with data in any formal sense. And I guess, you know, we can have our discussion of that, but it's a little different from addressing the questions where we've been given a lot of information.

We have a motion and a second. Is there any further discussion on the motion on the floor?

Okay, all in favor, say aye.

(A chorus of ayes.)

DR. GARBER: Opposed?

(No response.)

DR. RATHMELL: Abstain.

DR. ZENDLE: Abstain.

DR. GARBER: One abstention.

DR. ZENLDE: Two.

DR. GARBER: Two abstentions.

MS. ATKINSON: For the third question, "Is the evidence adequate to determine the clinical effectiveness of unilateral thalamic DBS for essential and/or Parkinsonian tremor for a well-defined set of Medicare patients with Parkinson's disease," two abstentions, and four fors.

DR. GARBER: And could I ask, for the

record, the people who abstained?

DR. ZENDLE: I abstained because I don't feel, as a non-neurologist, that I have enough information to say that there is adequate evidence, because it wasn't all presented and analyzed for us this time.

DR. RATHMELL: Yeah, mine exactly. I mean, I respect the testimony that's been given here on the floor, but, in terms of advanced preparation, we were just given the studies individually to synthesize on our own, and that's contrary to what we're usually given.

DR. GARBER: Right. Okay, thank you.

Now, we --

DR. HOLOHAN: Do you want explanations for the yes votes, or --

DR. GARBER: Okay, yeah. Go ahead, Tom.

DR. HOLOHAN: I supported it mainly because I read through, painfully, the extra studies submitted by Medicare on unilateral -- or labeled as unilateral stimulation, which, in fact, were, as described, a mixture of unilateral and bilateral. And I thought the evidence was reasonable, that it was effective and supported by the FDA's approval of the device for that indication.

DR. GARBER: Yeah, if I might just make a little comment here, I think it will be very helpful to us, whenever CMS wants us to look at any subgroup, either defined by the treatment or the population, that it's helpful to have the data broken out according to those subgroups, and, if they can't do it, to have a statement that it wasn't possible to do so we have this done in very clear terms. It's very confusing otherwise. You have to dig through and realize, as Tom did, that there's actually a mixture. So, in general, I think we can give better guidance to CMS if we get the data packaged in a way that enables us to make those distinctions.

Okay, so we, next, are asked to consider the size of the overall health effect. And I think we already heard one statement about it. But any discussion or a motion with regard to the size of the overall health effect?

DR. BURCHEIL: I would move --

DR. GARBER: Is this a suggestion?

DR. BURCHEIL: -- I would move that this be placed in the same category, that it's substantially more effective.

DR. HOLOHAN: Second.

DR. GARBER: Okay. Any discussion? All in favor?

(A show of hands by Dr. McBryde, Dr. Sigsbee, Dr. Burcheil and Dr. Holohan.)

DR. GARBER: Opposed?

(No response.)

DR. GARBER: I guess -- we may need to know. I'm not sure we know.

DR. ZENDLE: Two abstained.

DR. GARBER: Two abstentions, again? Okay, well, that makes sense.

MS. SAMUELSON: I would like to, for the record, just echo what you said about -- about recommendations on providing the data in a clear form, because my impression is this will have an important and negative effect on the patient population and the much larger patient population with essential tremor because of the extra cost and risk and simply the physical burden of two surgeries.

DR. GARBER: Thank you.

We have three discussion questions. I think we've implicitly discussed a good bit of one and two, and we've had a lot of discussion, but no conclusion, about the third. And would it be

appropriate, Perry and Steve, if we went to the third about who should -- this is basically about who should be considered qualified to carry out the procedure. Is that where -- (inaudible) -- at this point?

DR. ZENDLE: Does CMS really need that guidance?

DR. PHURROUGH: We'd like guidance in all three. The --

DR. GARBER: Okay. We can take them in order.

DR. ZENDLE: Have we received enough, is the question, in the discussion already?

DR. PHURROUGH: Um --

DR. ZENDLE: Because we're not going to vote on these.

DR. PHURROUGH: Actually, we've had significant discussion on one and three.

DR. GARBER: Well, the issue in number two -- and this did come up a little bit on the phone conversation as -- it's kind of difficult to answer. If you take the whole body of evidence, it's hard to know what you mean by "closely matching the patient," because the -- and I think this is part of the sense of the discussion. We had fairly diverse

patient populations included in the study, so the question would be, Who might be a candidate who was not represented in the studies?

DR. LITVAN: I think that there -- in most of the studies, they use the same criteria. That is basically what it was -- has been said here -- that is, patients that do have Parkinson's disease, according to current criteria, that have failed medical treatment but still have some benefit from levodopa therapy, and they don't have other contraindications, they don't have dementia. And I think -- et cetera -- all these are in the literature -- I mean, in every study that you see. And I think that that would be the patient population that this should be indicated.

DR. GARBER: I guess maybe -- then that -- a contrary would be someone who has not failed medical therapy. They are not represented. And does the panel want to address that group of patients? That's the sort of thing you have in --

DR. BURCHEIL: Can you generalize this outside the conclusion criteria, which, as Dr. Litvan said, is fairly consistent --

DR. GARBER: Right.

DR. BURCHEIL: -- among all the studies.

DR. GARBER: And we did hear a little bit already from the panel on that question. But does anybody want to make statement about that?

DR. LITVAN: Well, I think that you cannot, because that -- for that, we don't have any evidence. And what we have is that there are -- there are no good responses. I mean, if you include patients that are demented, or if you include patients that have other diseases, or if -- you know, if you start opening this up to a different patient population than the one that really has been giving us the evidence.

DR. BURCHEIL: Not only don't we have evidence, but it's not likely we're going to get that kind of evidence. I mean, even the new study coming up is going to take patients in at a medically intractable level. So --

DR. GARBER: I think you have a fairly consistent set of comments here from the panel on that question.

DR. BURCHEIL: So on the flip side of that, if -- what happens to that group of patients that may benefit? That if we say, yeah, we favor you, sticking close to the characteristics, and if they then limit it to exactly those criteria,

they're going to --

DR. GARBER: I think the question was whether there would be --

DR. LITVAN: Well, one thing is indications, another thing is characteristics. For example, characteristics is that the age group was a little bit -- you know, there was a problem with the age group at surgery. And that's not exactly what we're saying. There is -- what we're saying is that the age group is larger than just those that have been indicated. But, on the other hand, the diagnosis has to be restricted, and there has to be no other complications and things like that. So it's not exactly close to in every respect.

DR. RATHMELL: Yeah, I hear what you're saying, but the problem is they're going to have to take this and make a list of criteria, and they'll say, well, age, no, the panel didn't think -- but, in terms of response to levodopa, that was very important. So how do they make the distinction between one and the other?

DR. BURCHEIL: I think this is one of those things that has hit a pretty good consensus now, that most of the local carriers have a -- (inaudible) -- about three or four -- I mean, you

know, Parkinson's disease, previously levodopa-responsive, now medically intractable by the definition, which may vary, but probably, ideally, should be an accomplished center, and not demented to the point of nonfunctionality. And I don't know if -- there's no hard number been assigned to that.

So, I mean, those are the entry criteria, and I thought the question was whether patients could be taken earlier than that. And that -- we sort of touched on that issue. A patient who says, "You know what? I don't want to take those drugs. I just want to go right to the stimulator," you know, as soon as they developed their first tremor. And I don't -- I think that we have -- we are -- we don't have evidence on that, and we're not likely going to get evidence on that in the near future.

DR. RATHMELL: And we're comfortable interpreting the inclusion criteria of the articles and your recommendation that we don't generalize it outside those inclusion criteria.

DR. SATYA-MURTI: Most carriers have a set of inclusion criteria based on one publication or another, many referring on the New England Journal. You could, again, gather them together or task it to some of the carriers to put together.

And one other criterion we require is that there not be a focal lesion identified by imaging studies. In other words, if there was a lacunar infarct in the region where the stimulation was going to take place, then we don't know what the effect would be. So there are common criterion, and they're very comparable among all carriers now permitting -- (inaudible).

DR. PHURROUGH: There's a part of Question 1 that I don't believe we've touched on today that I'd like to discuss just briefly. Most of the studies talked about patients who had early-onset Parkinson's disease. And is there a difference in patients who have early-onset Parkinson's, versus those who have late-onset Parkinson's? And would DBS be used differently in those two different population groups?

DR. BURCHEIL: I've always found onset identification to be very difficult. That's just the age question turned around.

DR. SATYA-MURTI: No, it's not really how old you are. It's how old you are when you get the disease. It's not when you -- (inaudible).

DR. BURCHEIL: Right. It's the length of disease. And advance -- treatment -- you know, the

stage of the disease.

DR. PHURROUGH: And obviously, there isn't evidence, but it -- using you as a group of expert panelists, is there any way to differentiate that group or treat them identically?

DR. LITVAN: No, the treatment would be the same. I think it's a question of age, the amount of time to get to surgery, and that's -- and still be below age 75.

DR. GARBER: I guess, Steve, is your question -- it's really -- granted that there's no direct evidence on the question, or inadequate direct evidence -- what should our presumption be, that there is or is not a difference? And I might add that's after controlling for other clinical characteristics, like the severity of the disease and whether they had responded to medications. Is that what this statement's getting at?

DR. PHURROUGH: Yes.

DR. GARBER: So is there -- should there be a presumption that it will be equally effective, knowing that there isn't direct -- or is there a presumption that it's also effective knowing that there's not direct data on the point?

Tom?

DR. HOLOHAN: Is there any evidence that drug-therapy effectiveness differs according to early- or late-onset Parkinson's disease? I'm -- we have a whole bunch of neurologists here, I'm --

DR. PHURROUGH: That's the main purpose for the questions, because we had a whole bunch of neurologists.

DR. LITVAN: There is no evidence. And there is no evidence --

DR. PHURROUGH: So if --

DR. LITVAN: -- it is -- we're talking about --

(Inaudible colloquy.)

DR. HOLOHAN: I don't think we can answer the question. You could turn it around and say there is no compelling evidence against generalizing the benefit to late onset versus early onset.

DR. GARBER: Yeah, I think that -- Steve, one of the issues here is -- at least with the surgery -- with the DBS for the elderly versus the young -- we had inadequate evidence, yet it raised some red flags, okay, and I think one question is, are there any red flags, or is there just no reason at all to think there's a difference between early and late onset, in terms of response?

Dr. Montgomery?

DR. MONTGOMERY: I'm sorry. Actually, a few years ago, Joe Jankovic did the study where he looked at early onset versus late onset and did find some mild differences in terms of the percentage that have tremor and the percentage that have postural gait instability and dementia. And the results were -- they were statistically significant, but huge overlap.

We subsequently did a longitudinal prospective study at the University of Arizona looking at age of onset in terms of symptomatology, responsiveness to medication, and really found no significant difference in early onset versus late onset. The big issue was the duration of the disease, per se. And I think -- so I think that there really is no significant difference in terms of the responsiveness to therapies.

DR. GARBER: You know, the thing to always keep in mind is, Does this add independent information, as compared with all the other clinical characteristics that you have? And that may be what's critical here, perhaps, how severe it is at the time that you're considering the treatment.

So is that enough of a --

DR. PHURROUGH: I think so.

DR. GARBER: Okay. So I would like to return, though, to the provider criteria. And I had the sense that we actually had -- there were several themes that came up repeatedly in our earlier questioning, and this is something that people are very interested in, obviously, because we jumped right into it, and that included having a multidisciplinary team, some amount of experience on the part of the neurosurgeon, but also it sounded like having experienced neurophysiologists, electrophysiologists, and so on.

So I guess the issue is, How detailed should we be in providing guidance about this? And what more can we say on the issue?

DR. WEINER: To go back to what was said earlier, I think that this part of it should be as nonspecific as possible because of the rapid evolution that's going on in the field. And if one wanted to say some words about the neurosurgeon and the neurologist, that would be fine, but -- I mean, it's conceivable in a few years electrophysiology might be replaced by another technique that is better than that. So I think we have to be careful about being very specific about beyond the team

members, the neurologists, and the neurosurgeon.

DR. GARBER: Well, you know --

DR. LITVAN: It has to be --

DR. GARBER: -- I have to point out one thing here, which is that when we look at procedures, the -- one of the issues in whether you have to have a highly specialized facility is how dangerous it is. And I must say, although people have said that this actually a fairly safe procedure, the numbers suggest it's not a very safe procedure in the sense that there's a high rate of fairly serious side effects in at least some of the studies. It may be fair to say, however -- and I believe this is really true -- that the risks are very acceptable in relation to the benefits.

But when you have something that's got substantial risk with something like hemiplegia and hemiparesis, that's when you start to say, well, we really should look into making sure it's done in places that have low complication rates. So I think that's part of the motivation for not being truly laissez faire about who should do the procedure. I'm sure that's part of CMS's concern.

I think -- maybe we should just go around the table, since there's so many hands up.

Bruce?

DR. SIGSBEE: Again, I think we have to be careful, because the other side of this is access. And that, for institutions who may legitimately want to get started, they're not going to have a track record. And if you require a track record before you will pay for it, you may preclude medical beneficiaries from having adequate access.

So there's the flip side to this, and I think you have to be very careful about who does this, but there also is a role for physicians making reasonable judgments, and I think Dr. Montgomery is right, is that the large majority of physicians make good judgments about what they can and can't do or should and shouldn't do. There's a few -- (inaudible), but not very many. And how can you put quality into a regulation? I think it's a little bit hard.

DR. GARBER: Kim?

DR. BURCHIEL: It's kind of hard not to be -- not to at least acknowledge what's been said, that this is a difficult procedure. It goes beyond the usual training of a neurosurgeon and I -- and, frankly, most neurologists. It's -- it requires a specialized team.

I think somehow, either at the level of CMS or the local carriers, there are going to have to be criteria for what defines a center, because I'm, personally, very nervous about the idea of this proliferating into centers that do a few of these a year, in which case the surgical techniques won't be as well worked out, and the experience won't be there, and there's a -- and we're basically living in a perpetual learning curve.

And the other thing that we find with this procedure is, if the technique is difficult, the follow-up is more difficult. It requires a huge amount of effort by medical practitioners, physicians, nurse practitioners, and others, because the outcome ultimately on this may make -- may have more to do with how closely these patients are followed and adjusted than they do exactly where the electrode is in the subthalamic nucleus.

So I do think we can't be mute on this. I think CMS needs to think about some criteria for training and experience.

DR. GARBER: Phyllis?

DR. GREENBERGER: I was wondering if any of the local carriers had certain requirements, and whether there's been any comparison within the

states and outcomes to know whether, in fact, those were realistic and necessary?

DR. SATYA-MURTI: I can address some of that. The local carriers -- we do ask for criteria along these lines, that there ought to be previous experience. And other medical directors call me and ask -- either they duplicate the same language or, as I said, the majority of the person -- the neurologists and neurosurgeons, their time should be devoted to performing this type of surgery or this type of evaluation. I haven't put down any percentage. So that seems to be one de facto way of making sure that this does happen in the right hands.

And the second would be that, for those new centers Dr. Sigsbee mentioned, I have often advised that it need not be, from day one, that the new center person has to have experience, but if you retro-activate that and say that they ought to have performed 12 of 15 or 20 within the past two years, this would enable those who have taken the training and taken a year to establish the program.

So, in practice, if you leave it at the carrier level, there are ways of getting around it, and if you so authorize the carriers to do so. So

we have ways of survival.

DR. GARBER: Tom?

DR. HOLOHAN: You know, actually, this really isn't new for CMS, formerly, when they were wearing their HCFA uniforms. The same process was used for approval of centers to do liver transplantation. Medicare put together an outside board of experts whose only job was to develop appropriate criteria for them. And a similar approach was followed -- I don't know if this was in the coverage manual or not, but, when they covered carotid endartorectomy, it was approved for use in centers that had less than 3.1 percent mortality rate for that procedure, which is -- appears, from the literature, to be the cutoff for risk and benefit. So --

DR. SATYA-MURTI: There is precedence, yeah.

DR. HOLOHAN: Right, I -- I think, certainly -- the only question we're asked is, Should there be criteria to perform DBS? And I -- I'm getting the impression it's the general view of the panel that, yes, there should be criteria. I realize everybody has to do something the first time, but low volumes of technically demanding

procedures are generally not a good thing.

And there was a comment -- a question, I think, to Medtronic about marketing. I think Dr. Zendle raised that question. Oh, I'm sorry -- Dr. Sigsbee.

Back when Medicare was debating covering laparoscopic surgery, there were organizations that gave certificates of proficiency in laparoscopic surgery to surgeons who attended a video course. These people could then take this back to their hospital credentialing committee -- privileging committee, and get privileges to do laparoscopic surgery. And I'm not implying that this would happen here, but it has happened in the past.

DR. GARBER: Ken?

DR. BURCHIEL: Well, actually, Kim made most of my comments, so I'll keep this brief, but I think we do need some general guidelines. We talked a lot about qualifications as a surgeon -- number of implants, for example -- but, as Kim pointed out, the surgical technique is only one side of this triangle that I view this process as. There's patient selection as one side, surgical technique as a second, and then patient management after the surgery as a third side. And just like you can't

have a triangle without three sides, you can't have a good outcome with this technique without having each of those three components.

Accordingly, I think it's important that we look at qualifications of the implanting center, which includes: Do they have the proper equipment, the proper facilities? Do they have a qualified neurologist? Do they have a qualified neurosurgeon?

I think what we need to strive toward accomplishing is to reduce, or perhaps eliminate, those centers or physicians who would dabble in this therapy, kind of the casual implanter, the one who does just a few or a handful each year. And we should promote the idea of centers of excellence to -- which we believe would promote good outcomes. And realizing that access is important, we need to give some leeway to get the new centers up and running.

DR. LITVAN: Well, I fully agree with what you said. I mean, all the points I was going to make were made. The only thing I would add is that I think that for new centers -- or even for those established, too -- perhaps there could be some kind of evaluation on a -- I don't know how you can do that, but on the degree of -- on the outcome, in

fact. And if they have mortalities or paresis or intracranial hemorrhage, whatever they do more than the average amount on a year basis or every two years or whatever.

DR. GARBER: Yes. Angus?

DR. MC BRYDE: Well, I was just going to say, like so many things in the cardia area and orthopedics, renal transplants, you've got to look at the infrastructure. You look at the people that are doing it. They need to be in depth. You've got to have a neurologist trained, neurosurgeon trained, you've got to have a hospital that's got a full-service subspecialty availability, you've got to have a radiology department that's got the in-depth MRI 3-D capacity, not just for this, but available in other areas. So it's in the infrastructure and it's the team that you could look. You can do pretty well with this, like you can with the early days of cardiac bypass, whatever.

DR. SIGSBEE: Can I make a motion that the answer to the question is yes?

(Laughter.)

DR. GARBER: Les?

DR. ZENDLE: Yeah, I agree with that. I would just add one thing, though, and that's that

this is very consistent with the recommendations from the Leapfrog Group, which is looking at the volume of certain surgical procedures. It is somewhat controversial in that there isn't always good data as to what the number should be and what the outcomes are, but I really think that as we address the patient safety and quality issues in this country, we need to move in that direction, and I think CMS ought to be joining Leapfrog and the other groups that are moving that direction.

DR. GARBER: Jim, did you have -- okay, I don't think we need a formal vote on this.

DR. ZENDLE: Move we adjourn.

DR. GARBER: Yeah, we will entertain a motion for adjournment.

Is there any other announcement? Steve, did you want to make an announcement?

DR. PHURROUGH: Yeah, I just want to thank the panel for their time, both the voting members and the guests. This -- your recommendations will be forwarded to the executive committee, and, at present, that's scheduled to be --

DR. GARBER: July 17th.

DR. PHURROUGH: -- September 25th.

MS. GREENBERGER: Once it goes to the

executive committee, then, I'm assuming they vote positively, how long does it take for it actually to be, you know, an official coverage decision and --

DR. PHURROUGH: We will then write our coverage decision after that meeting. We have a maximum of 60 days, though I suspect it will not take us that long. And then once we write our coverage decision, then Medicare has to write instructions. Those instructions are only released once a quarter. So we're probably talking about instructions to the contractors, carriers first of the year.

MS. GREENBERGER: And then what happens in terms of the termination of the level of reimbursement?

DR. PHURROUGH: We don't get involved. Since it's already performed now, I don't suspect there's -- will be reimbursement issues. They'll be reimbursed as they're being reimbursed now.

MS. GREENBERGER: I think it varies.

DR. PHURROUGH: If people think they're being reimbursed well enough now, that's an entirely separate issue that coverage doesn't get involved in.

DR. GARBER: Before people vote with their

feet, I would entertain a motion so we could have a formal vote on adjournment.

DR. ZENDLE: So moved.

DR. SIGSBEE: Second.

DR. GARBER: All in favor?

(Chorus of ayes.)

DR. GARBER: Thank you, everyone. Thank you to the speakers and -- the public speakers and our invited speakers. Thank you to the panel.

[Whereupon, at 12:25 p.m., the meeting was adjourned.]